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Abstract

The impact of opiate substitution treatment on mortality risk in drug addicts: a natural experiment study

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Background: Opiate substitution treatment (OST) is the main treatment for people addicted to heroin and other opioid drugs. However, there is limited information on how the delivery of this treatment affects mortality risk.

Objectives: To investigate the associations of mortality risk with periods during treatment and following cessation of treatment, medication type, co-prescription of other medication and dosing regimens during titration and detoxification. The trends with time of prescribed medication, dose and treatment duration were also explored.

Design: Prospective longitudinal observational study.

Setting: UK primary care between 1998 and 2014.

Participants: A total of 12,780 patients receiving methadone, buprenorphine or dihydrocodeine.

Main outcome measures: All-cause mortality relating to 657 deaths and drug-related poisoning relating to 113 deaths.

Data sources: Clinical Practice Research Datalink with linked information on cause of death from the Office for National Statistics.

Results: For both outcomes, the lowest mortality risk was observed after 4 weeks of treatment and the highest risk was observed in the first 4 weeks following cessation of treatment [e.g. for drug-related poisoning, incidence rate ratio (IRR) 8.15, 95% confidence interval (CI) 5.45 to 12.19]. There was evidence that the treatment period risks varied with OST medication. The largest difference in risk was for the first 4 weeks of treatment for both outcomes, with patients on buprenorphine being at lower risk than those on methadone (e.g. for drug-related poisoning, IRR 0.08, 95% CI 0.01 to 0.48). The co-prescription of benzodiazepines was associated with linearly increasing the risk of drug-related deaths by dose (IRR 2.02, 95% CI 1.66 to 2.47), whereas z-drugs (zolpidem, zopiclone and zaleplon) were associated with increased risk of both all-cause (IRR 1.83, 95% CI 1.59 to 2.12) and drug-related (IRR 3.31, 95% CI 2.45 to 4.47) mortality. There was weak evidence that higher initial and final doses were associated with increased all-cause mortality risk. In the first 4 weeks of treatment, the risk increased by 4% for each 5-mg increment

in methadone dose (1-mg increase in buprenorphine) (hazard ratio 1.04, 95% CI 1.00 to 1.09). In the first 4 weeks after treatment ceased, a similar increment in final dose increased the risk by 3% (hazard ratio 1.03, 95% CI 0.99 to 1.07). There were too few deaths to evaluate the effects on drug-related poisoning. The proportion of OST patients receiving buprenorphine increased between 1998 and 2006. Median treatment duration was consistently shorter for buprenorphine than for methadone for each year studied (overall median duration of 48 and 106 days, respectively).

Limitations: As this was an observational study, the possibility remains of bias from unmeasured factors, which covariate adjustment and inverse probability weighting can eliminate only partially.

Conclusions: Using buprenorphine as an alternative to methadone may not reduce mortality overall despite resulting in lower IRRs from shorter treatment duration. Clinical guidance needs to consider strengthening warnings about the co-prescription of a range of drugs for OST patients.

Future work: Our analyses need to be replicated using other clinical data sets in the UK and in other countries. New interventions and trials are required to investigate improving the retention of OST patients in primary care.

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List of abbreviations

ACM	all-cause mortality
CI	confidence interval
CPRD	Clinical Practice Research Datalink
df	degrees of freedom
DRP	drug-related poisoning
GP	general practitioner
HR	hazard ratio
ICD-9	*International Classification of Diseases*, Ninth Edition
ICD-10	*International Classification of Diseases*, Tenth Edition
IPW	inverse probability weighted
IRR	incidence rate ratio
IV	instrumental variable
NDTMS	National Drug Treatment Monitoring System
OST	opiate substitution treatment
PPI	patient and public involvement
PSM	propensity score matching
SCCS	self-controlled case series
SD	standard deviation
SE	standard error
WP	work package

Plain English summary

Users of heroin or other opioids, such as morphine, have a risk of death 10 times higher than that of the general population. Overdose is the most common cause of death. In England and Wales during 2015/16, over 1200 people died from opioid poisonings, the largest number on record. The most effective treatment for people dependent on opioids is the prescription of substitute drugs, usually methadone or buprenorphine, called opiate substitution treatment. In the UK, this treatment is delivered commonly in primary care, often with support from drug agency workers.

We analysed data from people on opiate substitution treatment in primary care. We assessed whether or not death rates (all-cause and overdose) change with different periods of treatment or between treatments, with buprenorphine compared with methadone, and with the co-prescription of other drugs such as benzodiazepines.

Mortality risk was lowest after 4 weeks of treatment, at 0.3% for overdose deaths, but it was eight times higher in the first 4 weeks after treatment ceased. There was evidence that mortality risk was lower for patients on buprenorphine than for those on methadone, especially in the first 4 weeks of treatment, when the mortality risk for the former was approximately 90% lower.

The co-prescription of benzodiazepines more than doubled overdose death rates. The co-prescription of other drugs (zopiclone and similar sedatives, and gabapentinoids) also increased the overdose risk by 60%.

Higher doses in the first 4 weeks of treatment may be associated with higher death rates. If patients dropped out of treatment rather than having their dose gradually lowered, this might have led to higher death rates in the first 4 weeks after treatment ceased.

The number of buprenorphine prescriptions per year has increased over time, but treatment duration is shorter for patients on buprenorphine than for those on methadone.

New interventions are required that retain patients on treatment in the community. Clinical guidance on the dangers of co-prescribing drugs with opiate substitutes may need strengthening.

Scientific summary

Background

Opioid drug misuse is a major concern in the UK, affecting up to 350,000 individuals. Opiate substitute treatment (OST) is a common and effective treatment, with methadone and buprenorphine being the two types of medication most often prescribed. Studies have shown an increased risk of mortality during the first few weeks at the start of treatment and in the period immediately following cessation of treatment. Only one study has examined how the risk profile may vary between methadone and buprenorphine, but as that study was based in Australia it is unclear whether or not a similar pattern of risk applies in the UK.

Clinical guidelines recommend a low initial dose and then increasing the dose over the first few weeks until a maintenance dose is achieved. Similarly, treatment should cease after a period of tapering doses, ending with a low dose. The guidelines also advise caution when using benzodiazepines with OST patients because of the possible drug interaction and the association of multidrug exposure with mortality.

Observational studies are prone to residual confounding related to causal factors that are omitted from the analyses or are poorly measured. Methods such as self-controlled case series (SCCS) are robust to such confounders, if their data do not vary with time, and may be helpful in identifying causal effects.

Objectives

This project aimed to address five main objectives associated with the five work packages:

1. To investigate the trends in the delivery of OST and how these relate to the clinical guidelines.
2. To explore factors affecting the risk of mortality, with particular reference to OST type and OST period.
3. To explore the effects of co-prescription on the risk of mortality among OST patients. Investigations considered not only benzodiazepines but also z-drugs and gabapentinoids.
4. To explore the effects of dose regimens during induction and during detoxification on mortality risk. Investigations considered regimens in terms of starting/ending doses and the change in dose over the first/last 28 days of treatment.
5. To investigate how SCCS methods might be modified in the context of OST and the implications of their results.

Methods

This study utilised data collected prospectively within UK primary care and administered by the Clinical Practice Research Datalink (CPRD). Four main types of information were extracted:

1. Patient sociodemographic information – this included basic information such as age and gender but also details about a patient's history of custodial sentences, alcohol problems and overdose.
2. Medications prescribed – this information was used to identify OST patients but also co-prescribed medications, such as benzodiazepines, that may affect mortality risk. Information on dose was also important.
3. Practice characteristics – this included information about the practice's location in the UK, and the practice size in terms of the number of general practitioners and the number of OST patients.

4. Date and cause of death – unlike date of death, cause of death was not routinely recorded within CPRD. However, data were linked to other UK databases, allowing cause of death to be extracted from an Office for National Statistics database. Unfortunately, at the time of this study, only about 50% of patients had been linked, limiting the patients eligible for drug-related poisoning (DRP) analyses. All patients were eligible for the analysis of all-cause mortality (ACM).

The identification of OST patients involved primarily those receiving at least 20 mg of methadone or 4 mg of buprenorphine at some time. Considerable efforts were made to exclude patients receiving these medications for pain relief. Patients receiving at least 480 mg of dihydrocodeine were also included when there was other evidence that these prescriptions were part of OST. In total, 13,005 patients were identified between the study dates of 1 January 1998 and 31 July 2014. In mortality analyses, up to 12,118 patients were utilised, reflecting those with ages between 15 and 64 years.

Poisson regression was the main method used to analyse mortality data. However, a variety of other methods and weighting of the data, most notably inverse probability weighting, were employed to obtain more robust results or were used as sensitivity analyses.

Results

The main results are listed below by objective. For objective 1, the main results on the trends in prescribing practice were as follows.

- Patients receiving OST may have reached a peak in 2008, with current numbers about 20% lower than at that time.
- The use of methadone within OST has been declining, whereas buprenorphine use increased up to about 2006. After this date, there was less evidence of any relative change in the use of these medications.
- The co-prescription of benzodiazepines declined during the study period while the co-prescription of gabapentinoids increased. The co-prescription of z-drugs did not change substantially during the study period.
- The average doses of both methadone and buprenorphine reached their maxima around 2008. Similarly, the proportion of episodes reaching an optimal maintenance dose improved up to 2008 but declined (methadone) or did not change (buprenorphine) after this date.
- On- and off-treatment duration generally increased during the study period. Buprenorphine had a shorter duration for both on and off treatment.

For objective 2, the results on OST type and mortality can be summarised as follows.

- Mortality risk was lowest during treatment after the first 4 weeks. Elevated risks were observed in the first 4 weeks of treatment and in the first 4 weeks following cessation of treatment.
- Differences between methadone and buprenorphine treatment were most pronounced in the first 4 weeks of treatment but also during the remainder of time on treatment, although the evidence was much weaker for DRP. Here, methadone had higher risks than buprenorphine. Potentially inconsistent results were obtained for the first 4 weeks following cessation, with ACM showing a protective effect for buprenorphine and DRP showing no difference, although the best estimate of the difference also showed a protective effect.
- The differences between methadone and buprenorphine for the 4 weeks after treatment had ceased were attributed to residual confounding, despite robust methods such as inverse probability weighting supporting this difference.
- The effect of OST type was observed to vary with age and comorbidity such that buprenorphine had stronger protective associations among older or more comorbid patients.

For objective 3, the main results on co-prescription and mortality were as follows.

- Co-prescription of benzodiazepines increased the risk of mortality for DRP.
- Co-prescription of z-drugs increased the risk of mortality for ACM and DRP.
- Co-prescription of gabapentinoids increased the risk of mortality for ACM, DRP and non-drug-related deaths.
- Concurrent exposure of benzodiazepines and z-drugs increased treatment duration but did not reduce overall ACM or DRP mortality risk.

For objective 4, the main results of the associations of initiation and cessation regimens with mortality were as follows.

- Higher starting and ending doses were associated with increased ACM.
- Increasing the observation period from 28 days to 56 days did not change these effect sizes but increased the weight of statistical evidence as a result of the increased number of deaths.
- There was no consistent evidence that change in dose in the first or last 28 days affected the risk of mortality.
- There was no evidence that these effects varied with OST type.
- Too few deaths were eligible for DRP analyses to allow any reliable conclusions to be drawn.
- There was some evidence that adherence to guidelines with starting and ending doses was improving after 2007 compared with before this date.

For objective 5, the main results from the modified SCCS methods provide some support for the interaction between OST type and period. The Farrington method for ACM showed similar protective effects for buprenorphine during the first 4 weeks of both the start of treatment and after the end of treatment. However, there was no evidence of a similar beneficial effect after the first 4 weeks of treatment. The Kuhnert method for ACM provided weak evidence of an interaction but, with the wide confidence intervals, it was difficult to interpret. Both SCCS methods for DRP provided no evidence of an interaction but the wide confidence intervals may suggest that these analyses were underpowered.

Conclusions

Our findings provided a conflicting picture of overall mortality rates related to methadone and buprenorphine treatments. Although analyses of mortality data suggested a beneficial effect for buprenorphine and suggested advantages to prescribing buprenorphine, especially during induction, simulations based on DRP mortality rates under a scenario of induction with buprenorphine with methadone thereafter were more equivocal on the net effect.

All-cause mortality rates increased after the cessation of treatment. This may be the result of poor retention during detoxification in the final stages of treatment or poor coping mechanisms following the planned cessation of treatment. Both are likely to benefit from greater patient support.

Our data suggested that the co-prescription of benzodiazepines and z-drugs had a detrimental association with mortality. Although recent guidelines suggest caution in prescribing OST to patients with benzodiazepine dependence, this study suggests that the warnings should be extended to prescribing benzodiazepines and z-drugs to patients undergoing OST.

There was evidence that adherence to clinical guidelines on dosing, in particular low starting and ending doses, may help to reduce mortality. The results for change in dose based on a 28-day window were equivocal, but this may have reflected too short a period in which to assess changes in dose.

Our study was limited by the availability of data on the addiction severity, the quality of OST (e.g. the use of supervised consumption) and the extent of psychosocial support. It is possible that such factors may have confounded our results.

Further work is needed to replicate our findings. In particular, such studies could clarify the role of gabapentinoids on mortality risk and whether older or more comorbid patients benefit from buprenorphine treatment more than from methadone treatment. Larger population-based data sets or more specialised data sets on addiction may help to identify the role of initiation and cessation dosing regimens on drug-related mortality, which our study was underpowered to evaluate.

Funding

Funding for this study was provided by the Health Services and Delivery Research programme of the National Institute for Health Research.

Chapter 1 Context

Background

Opiate substitution treatment (OST) is the key treatment for heroin dependence and has been shown to have multiple benefits, including reducing drug-related crime and blood-borne virus transmission and improving social functioning, as well as reducing drug-related deaths.[1–5] Prescribed OST in the community includes primarily methadone but also buprenorphine and occasionally dihydrocodeine.[1,6] Clinical guidance advises that the choice of drug should take account of a number of factors, including retention and treatment compliance, the patient's preference and the clinician's experience with prescribing these drugs.[7,8] When the choice is unclear, methadone should be prescribed as the first choice.[8] In England there are approximately 350,000 opioid-dependent people and 150,000 people who inject drugs, although these estimates are uncertain as they can vary substantially by method of derivation and by source of information.[9–12] Of these people, about half are exposed to drug treatment annually, mainly OST (75%) but also non-pharmacological treatments delivered in specialist drug agencies and residential units.[9] OST is effective because it reduces illicit opioid drug consumption, in particular drugs used through injections, and is cost-effective because of the subsequent reductions in drug-related crime and health harms.[13] Observational studies[14–18] have shown that the risk of mortality is reduced during OST. Buprenorphine, hypothetically, is less likely than methadone[19] to cause fatal overdose, and in some studies it has been shown to be as good as methadone at treatment retention,[20] although in others the dropout rates were higher.[16,21–23] In France, ecological analyses suggest that trends in overdose deaths are negatively associated with increases in buprenorphine prescription.[24] However, there is little direct comparative evidence on the risk of death during buprenorphine versus methadone treatment, and none in the UK.

Several recent studies[15–17,25] have highlighted that there is a period of very high mortality risk in the first few months immediately after treatment cessation, which is at least eight times higher than the mortality risk during treatment. In the UK, analyses of primary care information have suggested that the risk of death in those who receive OST is twice as high among men as among women, is raised at the beginning and end of treatment, and may be higher in those co-prescribed benzodiazepines.[15,26] In Australia, the risk of death at treatment onset was greater than in the UK, with some evidence to suggest that the mortality risk at treatment onset was lower among those initiated on to buprenorphine than those initiated on to methadone, but these benefits may be offset by a shorter duration of treatment for those on buprenorphine than for those on methadone.[16] The evidence base for other drug treatments (residential rehabilitation, detoxification, and psychological treatments) is more limited, but studies also suggest that the risk of mortality is reduced during treatment compared with out of treatment, and is elevated within the first 30 days compared with > 30 days after treatment ceases.[17,27]

The effect of prescribing other medications to OST patients has also been studied. Research to date has focused on benzodiazepines, z-drugs (zolpidem, zopiclone and zaleplon) and gabapentinoids (gabapentin and pregabalin). Here, studies[26,28–33] have suggested that the prescription of these medications may increase the risk of mortality. Despite this, and against treatment guidelines,[34,35] many OST patients are prescribed these medications.[28,29]

Other aspects of treatment may also be important, such as additional psychological support, supervised consumption, titration up and tapering down of OST doses at the beginning and end of treatment, and take-home naloxone.[35] Clinical guidance recommends that, at the initiation of OST, patients are started on low levels of methadone or buprenorphine and then steadily increased to achieve an optimum level of prescription while minimising the risk of overdose.[7,36] The planned discharge of patients should involve gradually tapering doses to low levels while minimising withdrawal symptoms. Supervised consumption, at least initially, also is recommended to ensure compliance and reduce diversion.

In the UK, OST has expanded fivefold in the past 10 years to > 1800 kg per year (≈33.3 million doses per year).[37] The rate of methadone deaths per gram of methadone prescribed has fallen, coinciding with and attributed to the issuing and implementation of clinical guidelines recommending greater supervised consumption;[38] however, the overall number of opiate-related deaths has not declined.[39,40]

Need for further research

The management and expectations of drug treatment are evolving, with the current drug strategy and treatment guidance focusing on steps to improve 'recovery'.[41] Evidence, however, on the impact of different ways of delivering treatment on drug-related mortality is limited,[40] and this is essential for current and future policy. It is not the intention of current treatment guidelines to reduce patients' access to, or limit the duration of, OST. Indeed, the latest guidance emphasises that 'it is not acceptable to leave people on OST without actively supporting their recovery and regularly reviewing the benefits of their treatment . . . Nor is it acceptable to impose time limits on their treatment that take no account of individual history, needs and circumstances, or the benefits of continued treatment'.[41] Many of the sentiments expressed in this document are echoed in the latest Home Office guidelines.[42] Nonetheless, user groups do fear that a reduction in treatment duration may be a consequence of the promotion of recovery in some local areas. Clinical guidance also has been reissued since this study was completed, emphasising the importance of adjunct therapies (psychosocial support) to retain people in OST, prevent chaotic dropout and achieve multiple benefits of OST.[43] In addition, the guidance supports 'a more explicit focus on individually defined recovery journeys with an enhanced focus on keyworking and care planning that integrates support for pharmacological and psychosocial interventions, and peer engagement and mutual aid'. OST is primarily delivered in the community through primary care, often in shared care arrangements with drug agencies or solely in the care of community drug agencies.[30,44] Earlier studies have examined mortality risk in and out of treatment utilising routine data collected from community drug agencies [National Drug Treatment Monitoring System (NDTMS)].[30] However, NDTMS data may not record accurately the start and end of OST and historically NDTMS does not collect data on the dose or type of OST. In this study, therefore, we used Clinical Practice Research Datalink (CPRD) data to examine the mortality risk of patients with an opioid disorder in primary care.

Large-scale observational studies, combined with mathematical modelling, are the most feasible approach by which to address questions about mortality risk. Published trials of OST are underpowered and rarely measure mortality risk, making synthesis of their findings unlikely to be informative.[5] There are few large-scale existing observational cohorts that reliably and adequately measure the relevant outcomes and exposures[18] and no large-scale 'head-to-head' comparisons of buprenorphine versus methadone treatment. In previous studies in the UK, there was insufficient power to detect differences in the risk of death for patients on methadone or buprenorphine, and information on specific causes of death was unavailable, prohibiting the investigation of drug-related deaths.[15,26] In addition, the exposure (and the effect) of the co-prescription of benzodiazepines or other drugs was examined in only one study in Scotland.[26] Careful consideration of confounders in the analysis of observational cohorts, however, will be important. One of the key analyses is to compare mortality risk between people prescribed buprenorphine or methadone (i.e. OST modality), and it is likely that the characteristics of opiate users prescribed buprenorphine or methadone will differ, which may be lost in simple comparisons of the risk of death by OST modality exposure.[45] Propensity score methods may be helpful in providing a more robust comparison of modality than simple covariate adjustment.[46,47] More recently, self-controlled case series (SCCS) methods have been developed, which may also be helpful in addressing these issues of residual confounding.[48–50]

Thus, previous analyses need to be expanded to assess the effect of OST on drug-related poisoning (DRP) (as well as overall mortality), to assess how changing the delivery of treatment may influence the risk of death, and to use different methods to test and address issues of confounding.

Chapter 2 Aims and objectives

Our overarching hypotheses are that the impact of OST in reducing deaths from DRP is influenced by modifiable treatment-related factors (such as treatment duration, co-prescription of other drugs, treatment modality and dose, and dispensing arrangements). In addition, the benefits of OST in reducing drug-related deaths in the population may be outweighed or balanced out by other factors that increase the risk of mortality for subgroups of opioid users or for other aspects of treatment.

The aim of the study, therefore, is to add to the body of robust evidence concerning treatment-related factors to inform and improve treatment guidelines that can underpin the effective reduction of population drug-related deaths through primary-care-based intervention. This project will focus on the analysis of OST delivered in primary care using the analysis data from the CPRD.

Our main research questions and goals to be addressed include:

- Is there evidence that the delivery of OST in primary care has changed over time – specifically in terms of changes in average dose and percentages of patients receiving optimal OST dose; OST modality; number and percentages of patients undergoing a planned discharged over time; number and percentages of patients receiving co-prescription of benzodiazepines; and number and percentages of patients with evidence of supervised consumption? [work package (WP) 1]
- We shall determine the risk of overdose and death by treatment exposure and modality, relate these effects to the number of overdose deaths and coverage and duration of drug treatment in the community, and project what factors could reduce the number of drug-related deaths in the population. (WP 2)
- Does any difference in the risk of mortality between prescribed methadone or buprenorphine change with the period of treatment exposure? (WP 2)
- Is the risk of mortality increased in people who are co-prescribed benzodiazepines, z-drugs or gabapentinoids (pregabalin and gabapentin)? (WP 3)
- Is the risk of death at treatment onset and cessation reduced in patients with evidence of supervised consumption and planned discharge? (WP 4)
- Adapt the SCCS methodology, originally developed for assessing vaccinations on health outcomes, for use in medication-based treatment. (WP 5)

Work packages 1–5 are reported in *Chapters 4–8*, respectively.

Chapter 3 Methodology

This chapter describes all aspects of study design, data collection and data analysis.

Conceptual framework of study

Natural experiments or observational studies provide opportunities to study interventions for which ethical considerations may prevent a controlled experiment such as a randomised controlled trial.[45] Publicly accessible databases, such as CPRD,[51] provide a cost-effective strategy for investigating interventions in a UK-representative sample. However, the lack of control in the study design can introduce bias into the results, and care is needed when analysing these data.[45]

Clinical Practice Research Datalink

The CPRD is a large database of anonymised patient records from 674 general practices and > 11 million patients in UK, covering 7% of the UK population at the time of this study. It is broadly representative of the UK in terms of sociodemographic characteristics and has good validity and replicability in relation to chronic illness.[52]

The Clinical Practice Research Datalink can provide information on the patient (gender, year of birth, registration and transfer out dates with the primary care practice, and date of death if applicable), their history of prescriptions (including daily dose and duration), entries in the clinical notes (including information on comorbid conditions and psychosocial adversity), the prescribing general practitioner (GP) (via anonymous identifier) and the primary care practice (region, date after which data are considered up to standard, and last data collection date by CPRD).[51]

Study design

This study was a prospective observation study using CPRD. Data were extracted on patients prescribed methadone or buprenorphine in primary care between 1 January 1998 and 31 July 2014. These data were expanded to include patients prescribed dihydrocodeine when the clinical notes indicated evidence of substance abuse. Patients were eligible for inclusion in the study if they were aged 15–64 years at entry. Patients were followed up from the latest of the study start date, the patient registration date or the up-to-standard date. Follow-up ended at the earliest of the study end date, the last data collection date, the transfer out date, the date of death or 1 year after the last OST ended. OST patients were defined as having been prescribed a daily dose of at least 20 mg of methadone, 4 mg of buprenorphine or 480 mg of dihydrocodeine.

Participants

The data extracted consisted of all patients prescribed methadone or buprenorphine between the study dates with additional patients prescribed dihydrocodeine when there was some evidence of drug abuse from the clinical notes. Thus, the initial data set consisted of 50,151 patients, of whom 49,729 were prescribed methadone or buprenorphine at some time during the study. It was recognised that a large proportion of these were receiving treatment for pain relief. To remedy this, patient histories excluded any prescriptions on which the prescription text contained ‘pain’ (mainly affecting dihydrocodeine), where the form of medication was patches (exclusively affecting buprenorphine) or when the prescription preceded the start of OST (exclusively affecting dihydrocodeine). This led to 53% of the patients being excluded (*Figure 1*). With 20% excluded on dose criteria, the final number of valid patients was 13,005 (26%).

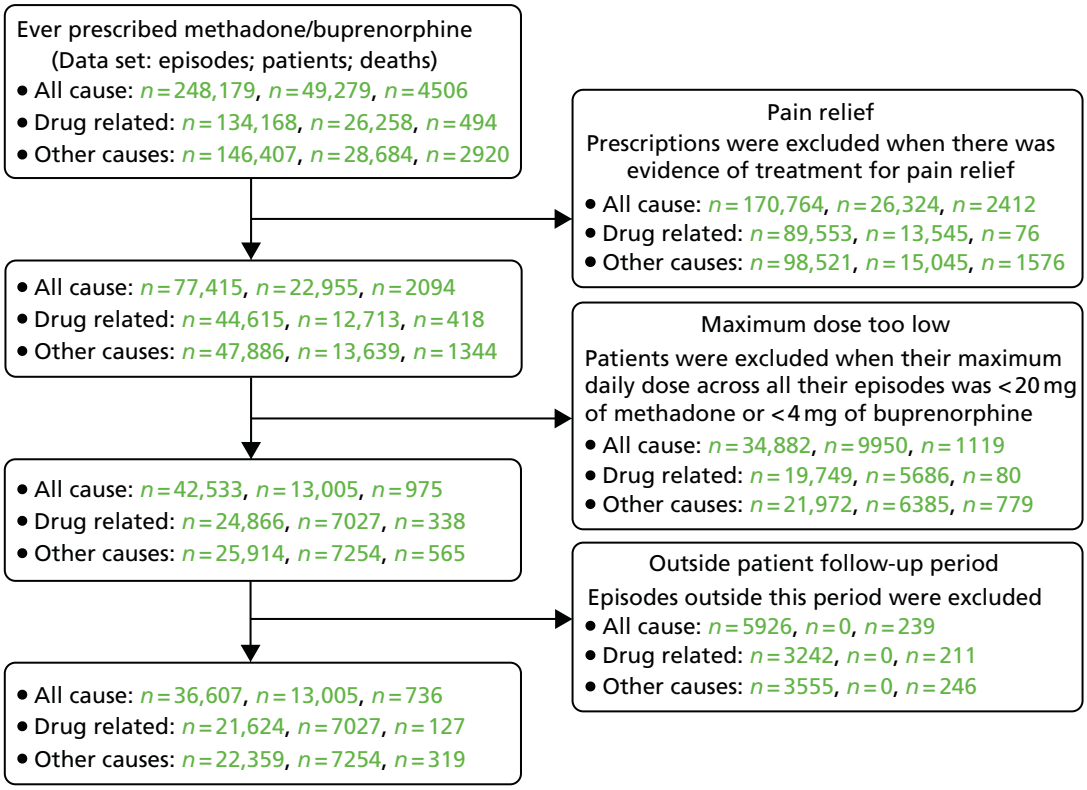

FIGURE 1 Flow chart of patients, episodes and deaths included in this study. This figure shows the numbers of episodes, patients and deaths for the all-cause, drug-related and other, non-drug-related, data sets. Prescriptions for pain relief were identified based on prescription text, medication in the form of patches or episodes of dihydrocodeine prior to starting OST. The follow-up period varied by patient and reflected a combination of the study period (January 1998 to July 2014), the patient registration period with the primary care practice, the CPRD usable data date and 1 year after the last treatment ended.

The number of patients varied between the WPs. The various exclusion criteria and the data relevant to each WP are shown in *Figure 2*.

Prescription daily doses, prescription duration and treatment episodes

Information on total quantity was present for 99.9% of prescriptions, reducing to 28% for daily doses and 9.1% for duration. Overall, complete information was available for only 2.2% of prescriptions, a further 32% having two items from which the third could be derived. To estimate the missing information for the remaining 66%, prescription patterns (such as other proximal prescriptions of the same quantity or trends in dosage history) were used to estimate daily dose, or prescription intervals were used to estimate prescription duration.

Opiate substitution treatment episodes were derived from patient histories when a gap of > 28 days existed between the expected completion of one prescription and the start of the next (all WPs). The CPRD sequence number, intended to indicate repeat prescriptions within a treatment episode, was set for only 50% of prescriptions in these data. Having derived treatment episodes, OST periods could be defined for each patient history. Four categories, as used in other studies,[15,53] were defined: the first 4 weeks of treatment, the remainder of any time on treatment, the first 4 weeks following cessation of treatment and any remainder of time off treatment.

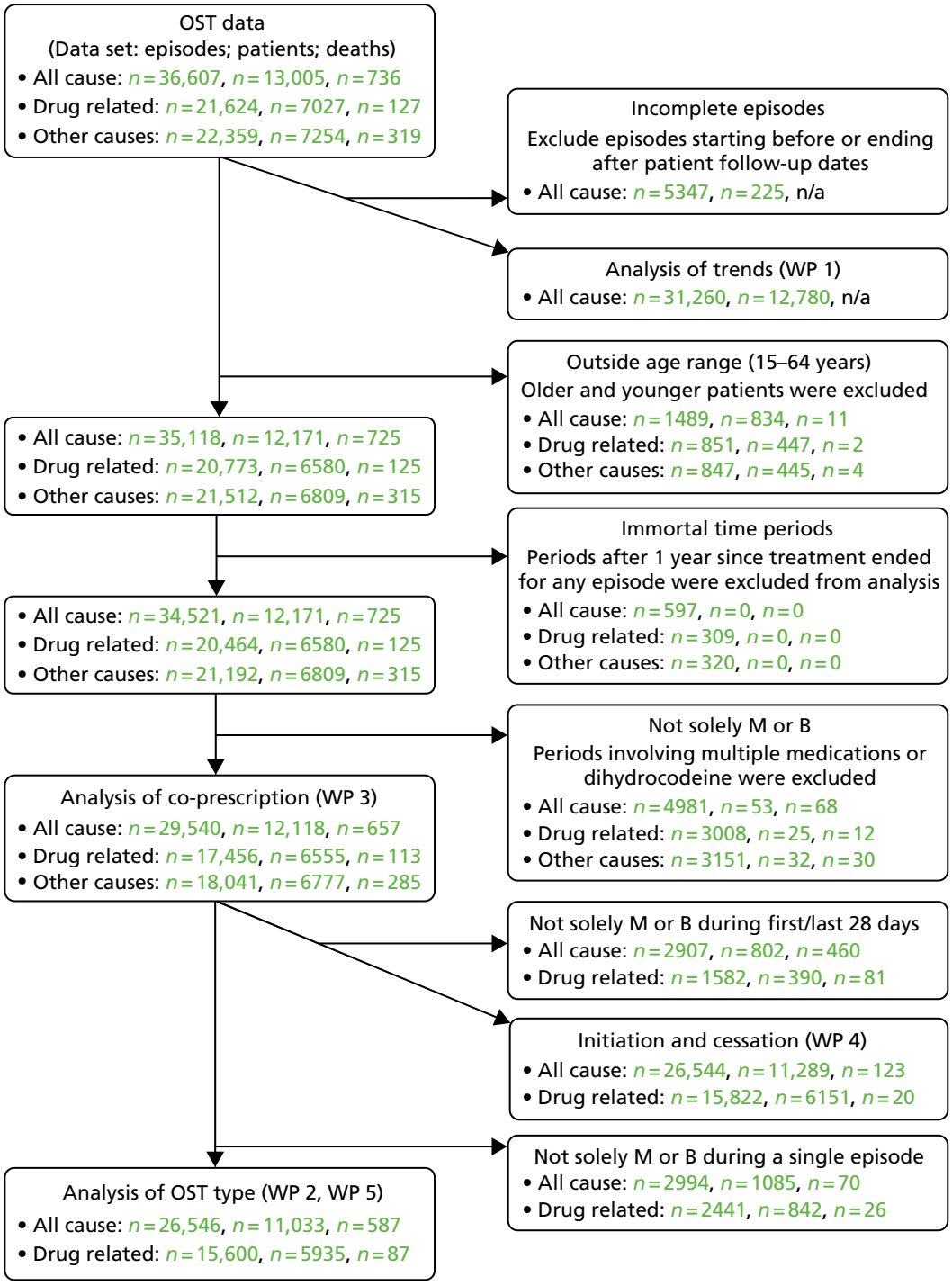

FIGURE 2 Relationship between the WPs in this study. B, buprenorphine; M, methadone; n/a, not applicable. WP 1 comprised the most data of all WPs, primarily because of the inclusion of dihydrocodeine episodes. Mortality was not analysed in this WP. The numbers quoted reflect minima used in the analyses of optimal doses. Other outcomes, such as the prevalence of OST, used the full OST data set. Other WPs restricted data to methadone and buprenorphine only, with WP 3 using the most data (any periods relating to these medications) and WP 2 using the fewest data (episodes of only one medication). The exclusion of periods > 1 year after the cessation of treatment for each episode (immortal time bias) affected the person-years at risk but not the number of deaths. The numbers for WP 4 reflect the combined total of all analyses, although in practice initiation and cessation used different data sets. Deaths relating to other non-drug-related causes were analysed in WP 3 only.

Episodes for benzodiazepines and z-drugs were generated in a similar fashion, but the gap between treatments was reduced to > 14 days to reflect the shorter expected treatment duration for these medications (WPs 1 and 3). Episodes for gabapentinoids were generated using > 28 days.

Main outcomes

The main outcome was date of death. For all-cause mortality (ACM), the date of death was obtained from CPRD. This was, to some extent, a derived variable extracted from various sources with varying degrees of accuracy. The most accurate was the death administration database, followed by statements of death as recorded in the clinical notes and, finally, the least accurate was the transfer out date with the reason given as death. CPRD has developed an algorithm for reconciling these sources of information.

Cause-specific mortality could be identified only for those patients linked to death certificate data supplied by the Office for National Statistics. Deaths from DRP were identified from the *International Classification of Diseases*, Ninth Edition (ICD-9) and *International Classification of Diseases*, Tenth Edition (ICD-10) codes.[54] These codes were supplemented to include more general, non-specific causes to reflect the potential under-reporting of DRP. The list of relevant codes is given in *Appendix 1*. The remainder of the deaths were classified as other, non-drug related deaths. No information on cause of death was available for patients from Scotland, Wales or Northern Ireland.

Main predictors

Opiate substitution treatment medication, particularly methadone and buprenorphine, and OST period were studied in WP 2. The period was defined to cover both periods of treatment (the first 4 weeks and the remainder of the time until cessation of treatment) and subsequent periods following the cessation of treatment (the first 4 weeks and the remainder of time until the next episode). This data set was also used in WP 5, where the modified SCCS methods were applied. The co-prescriptions of benzodiazepines, z-drugs and gabapentinoids were the main predictors in WP 3. Initiation and cessation doses were studied in WP 4, while year (1998 to 2014) was the main predictor in WP 1. Further details can be found in the specific chapters relating to each WP.

In WP 1, the main predictors and patient characteristics used in other WPs became outcomes in this WP as their trends across time were explored.

Main confounders

The main adjustment variables were age, gender, calendar year, comorbidity score and UK region.[15,16,26,55] Other potential confounders such as social class,[26,55] last treatment dose[15,55] or episode number[15] were omitted because of lack of any consistent evidence of an effect from these studies.

The comorbidity score was derived from 17 chronic illnesses.[56] A list of 3156 Read codes had been linked to these illnesses. These were translated to the current CPRD medcodes. This was possible for 2856 codes. A time-varying covariate was calculated based on information on the earliest onset of these illnesses and the weight given to each. The comorbidity score was derived by accumulating the weights across time for each patient. Although the score had a range of 0–11, in analyses, this variable was recoded to 0, 1 or ≥ 2.

In WP 3, OST type and period were used as additional adjustment variables.

Propensity scores

In WPs 2 and 3, propensity scores were generated for prescribed medications using logistic regression on four groups of variables.

1. Other prescribed medications. Propensity scores were generated for buprenorphine compared with methadone, and benzodiazepines, z-drugs and gabapentinoids compared with non-prescription. For each medication's propensity score, the other three medications were used as predictors. As buprenorphine was an alternative to methadone, its propensity score could be generated for each episode. For other medications, propensity scores reflected whether or not they were ever exposed during each patient's history of prescriptions.
2. Practice characteristics. General practices were described by the number of OST patients receiving treatment during each year of the study, the size of the practice and the UK region. The size of practice was defined by the number of GPs writing prescriptions, OST or other, in any one year, excluding those identified as locums. UK region was used in all analyses, and the other two measures were used solely in propensity score derivation.
3. Psychosocial adversity. Five measures of adversity were derived from the recording of relevant CPRD medcodes in the clinical notes (see *Appendix 2*). These data were used to generate non-time-varying binary variables reflecting any recoded event of self-harm, having ever taken an overdose, having ever had alcohol problems, having ever been in prison or having ever been homeless.
4. Main confounders. The five main confounders noted above were also included in the model.

These scores were used in inverse probability weighted (IPW) or propensity score matching (PSM) analyses.

Public and patient involvement

Interviews in small groups were conducted by two facilitators from the Bristol Drugs Project during 2015–16. These occurred in two geographical sites and involved multiple services (see *Appendix 3*). Focus groups with staff and service users explored their views and preferences around substitution therapy with methadone compared with buprenorphine and around considerations influencing their concurrent use of benzodiazepines, z-drugs and gabapentinoids. Service users were also asked for their views on the research questions we considered in this project in terms of the relevance of the questions, the priority they would attach to them and any additional questions that they felt were important. Where feasible, we used these views to inform our analysis plan.

Statistical analyses

Mortality data were analysed using Poisson regression (WPs 2 and 3). In WP 5, fixed-effect Poisson regression clustering on patients was used to analyse mortality data as part of SCCS analyses. The results of these analyses are reported as incidence rate ratios (IRRs). Mortality was also analysed using survival analysis (WPs 2–4). For these analyses, the risk of mortality was reported as hazard ratios (HRs). In unadjusted analyses for WPs 2–4, mortality rates are also reported. For WP 1, linear and logistic regression were utilised depending on the outcome. Further details can be found in *Chapter 4*.

A number of techniques were utilised in an attempt to provide estimates less susceptible to bias from residual confounding than those from standard adjusted Poisson analyses. The primary technique was IPW used in WPs 2 and 3. Simply, this method aims to emulate a randomised trial by utilising weights reflecting the inverse probability of receiving the observed treatment.[47] This has the effect of evenly distributing confounders between the exposure groups. PSM also attempts to balance confounders between the exposure groups, but here the balancing is achieved more directly by choosing observations from the two groups with similar propensity scores. In WP 2, PSM was applied to episodes of either methadone or

buprenorphine. Matching was achieved if the two episodes had their logits of the propensity score within 0.25 standard deviation (SD).[46] The third method was instrumental variables (IVs).[57] A valid IV is causally related to the exposure, related to the outcome only via the exposure and unrelated to confounders. Previous studies have utilised physicians' prescribing preference as an IV.[58,59] In WP 2, the prescribing GP's previous OST prescription was explored as an IV.

In WP 4, initiation and cessation dose characteristics were estimated for the first/last 28 days of each episode. Because death may have occurred during these periods, linear growth models were used to estimate the latent trajectories.[60]

On a technical point, it is worth commenting on the relationship between unadjusted mortality rates, IRRs and HRs. For standard Poisson regression, IRRs are identical to the equivalent mortality rate ratio, but for other analyses, this equality does not hold. Hence, Poisson regression clustering on patient will always adjust for patient differences. Similarly, in survival analysis, effects are always estimated relative to the survival function, which is usually related to age. Hence, although we refer to unadjusted analyses, models involving a single factor or covariate, it is important to recognise the implicit adjustment being made in some of these analyses.

Effect of opiate substitution treatment on drug-related poisoning mortality in the population

In WP 2, we estimated the probability that OST reduces DRP in the population by calculating weighted mortality risk ratios of DRP deaths. These mortality ratios compare the observed mortality risk in patients undergoing OST with the assumed mortality risk of opioid-dependent patients who do not enter OST (accounting for fluctuating mortality risk in different periods on and off OST, and for variation in the duration of current treatment). We also estimated the minimum duration of methadone and buprenorphine required to reduce DRP deaths in the population (for more details see web appendix 2 in that WP's main report[61]).

Research ethics approval

Ethics approval for this research project was obtained from Independent Scientific Advisory Committee, Medicines and Healthcare products Regulatory Agency (protocol 14–0732R2Mn2).

Reporting guidelines

This report follows RECORD (REporting of studies Conducted using Observational Routinely-collected health Data) guidelines for the reporting of observational studies.[62]

Chapter 4 Trends in opiate substitution treatment, patient characteristics and prescribing practice

Deaths from DRP were 50% higher in 2014 than in 1998.[54] This may suggest that there were major changes in the characteristics of those who abuse drugs and their treatment during this period. In this chapter on WP 1, we explore some of these changes.

Aims and objectives

In this WP, we aim to investigate how OST delivery has changed over time, in terms of:

- number of OST patients and episodes by OST type
- patient characteristics such as age, gender and medication prescribed
- episode characteristics such as mean and maximum dose and duration.

Details of the starting and ending doses are considered in *Chapter 7*.

Data set

The data used in these analyses were restricted to episodes in which some part of treatment occurred during the study period. To obtain a more accurate picture of the trends in these data, we considered all episodes including those involving dihydrocodeine or more than one medication and all patients ignoring the age restriction used in other WPs (see *Figure 2*). This led to the data for 12,780 patients and 34,427 episodes being analysed.

Prevalence of opiate substitution treatment

Crude UK prevalence estimates were derived from valid OST patients within each year and the total number of patients within CPRD. To obtain adjusted prevalence estimates, it was necessary to estimate the number of OST patients for the UK. This was achieved by combining numbers of patients for each country, taking into account the different coverages for each country by CPRD.

Patient characteristics

These outcomes include age and gender demographics and the medications prescribed. Medications included not only the three OST medications but also benzodiazepines, z-drugs and gabapentinoids. The last three medications were considered to be prescribed only during valid periods for each patient.

Episode characteristics

Mean and maximum doses were considered as outcomes. These are reported by year for episodes involving only methadone or buprenorphine. Average doses were calculated daily for the parts of episodes within any given year. Maximum doses were reported as a percentage of episodes with ≥ 60 mg for methadone or ≥ 12 mg for buprenorphine. The last episode for each patient was excluded if treatment was ongoing at the time follow-up ceased. This reduced the episode count to 31,260. For this outcome, episodes were valid only for the year associated with the maximum dose.

In addition, on- and off-treatment duration were investigated. Episode treatment was considered to cease when there was a gap of > 28 days between the end of one prescription and the start of the next. Last episodes were right-censored by the death of the patient, the last CPRD data collection date or the end of the study. First episodes were potentially left-censored by the practice up-to-standard date, the start of patient follow-up (registration with a CPRD practice) or the study start date.

Statistical analysis

A number of different analyses were used to assess trends depending on the particular outcomes. The prevalence of OST was analysed using Poisson regression. Binary outcomes (gender, medications and dose criteria) were analysed using logistic regression. Trends in duration were analysed using survival analysis to take account of censoring. Different parametric distributions were compared to find the best fit (*Table 1*). These analyses suggested that the log-normal distribution was superior, although other distributions gave similar results. Other outcomes, namely age and mean dose, were analysed using linear regression.

Primary analyses involved unadjusted year effects. Trends were assessed in two ways. First, a linear year effect was fitted to the data. Second, a deviation statistic was calculated. This reflected twice the difference in log-likelihoods between a model treating year as a factor and the linear model. The derived statistic [15 degrees of freedom (df)] provided evidence of any non-linearity. Where the analysis involved linear regression, the trend is additive from one year to the next. For other analyses, there is an implicit log transformation making the trend a multiplicative effect from one year to the next when back transformed.

Trends in prevalence of opiate substitution treatment

Most countries in the UK showed similar trends in that OST prevalence rates and number of patients were increasing at the start of the study and declining by the end (*Table 2* and *Figure 3*), although for Northern Ireland, where the use of primary care to treat problem drug use is more limited, these data were underpowered to detect the possible inverted U-shaped trend. The observed maxima varied by country and ranged between 2008 and 2011 for three nations, with Scotland showing an earlier peak, in 2003. Overall, the UK showed a maximum in 2008. Perhaps as expected, the adjusted UK estimates were similar to the unadjusted estimates because of the major contribution of England to the UK total.

TABLE 1 Comparisons of parametric survival functions for the analysis of duration

	Duration model log-likelihood	
Function	On treatment	Off treatment
Gompertz	–52,482	–34,247
Log-logistic	–49,384	–33,199
Generalised gamma	–48,827	[a]
Exponential	–57,672	–35,245
Weibull	–50,558	–34,372
Log-normal	–48,900	–32,415

a This model failed to converge.

TABLE 2 Prevalence of OST by country and year

	CPRD coverage by country (%)					Prevalence by country[a]					UK adjusted	
Year	England	Wales	Scotland	Northern Ireland	UK	England	Wales	Scotland	Northern Ireland	UK	Prevalence[a]	*n*[b]
1998	4.61	6.36	3.19	4.71	4.57	4.04	1.94	12.34	0.96	4.32	4.58	28
1999	5.70	8.35	3.87	5.57	5.66	4.72	3.17	11.96	1.32	4.94	5.18	32
2000	6.40	10.01	4.52	6.97	6.43	4.86	3.32	12.75	1.13	5.11	5.36	33
2001	7.00	11.41	5.85	7.87	7.15	4.89	3.23	14.53	1.22	5.33	5.54	34
2002	7.45	11.63	7.13	8.82	7.66	5.24	3.96	15.60	1.15	5.84	5.96	37
2003	7.45	12.48	9.05	8.85	7.87	5.61	4.93	17.11	1.01	6.53	6.42	40
2004	7.68	13.06	9.46	9.21	8.14	6.05	5.36	16.87	1.15	6.91	6.80	43
2005	7.75	13.34	9.54	9.24	8.22	6.65	5.94	17.02	1.45	7.46	7.35	46
2006	7.87	13.33	9.64	9.21	8.32	6.96	5.87	13.99	1.62	7.40	7.35	47
2007	7.94	13.96	9.65	9.12	8.42	7.35	6.57	12.87	1.61	7.65	7.62	48
2008	7.79	13.99	9.63	8.43	8.26	7.64	7.44	12.90	1.41	7.97	7.90	51
2009	7.65	13.98	9.62	8.37	8.15	7.51	7.23	13.08	1.28	7.86	7.79	50
2010	7.51	14.00	9.61	8.36	8.02	7.40	7.57	14.86	1.27	7.98	7.86	52
2011	7.22	14.02	9.69	8.33	7.78	6.82	7.89	14.51	1.46	7.55	7.36	49
2012	6.92	14.11	9.68	8.34	7.54	6.67	7.59	13.02	1.38	7.26	7.09	47
2013	6.76	14.64	9.68	8.34	7.43	6.18	6.55	12.78	1.31	6.78	6.61	44

continued

TABLE 2 Prevalence of OST by country and year (*continued*)

	CPRD coverage by country (%)					Prevalence by country[a]					UK adjusted	
Year	England	Wales	Scotland	Northern Ireland	UK	England	Wales	Scotland	Northern Ireland	UK	Prevalence[a]	*n*[b]
2014	5.93	14.37	9.74	8.34	6.72	5.16	5.05	12.31	1.05	5.87	5.64	38
Trend[c]						1.023	1.050	0.989	1.009	1.022	1.020	1.026
SE (trend)[c]						1.18	4.12	2.20	12.32	1.01	0.26	0.26
p-value						< 0.0001	< 0.0001	< 0.0001	0.4786	< 0.0001	< 0.0001	< 0.0001
Deviation						< 0.0001	< 0.0001	< 0.0001	0.9747	< 0.0001	< 0.0001	< 0.0001

SE, standard error.
a Prevalence rate (per 10,000 patients).
b In thousands.
c Trend is multiplicative.

Notes
Approximate SEs are reported multiplied by a factor of 1000.
Prevalence estimates were calculated as the observed number of OST patients divided by the number of CPRD patients. For the UK, an adjusted prevalence rate estimate was calculated from the expected OST patients for each country within the UK (using the CPRD coverage) and the number of UK-registered patients (see *Appendix 4*).

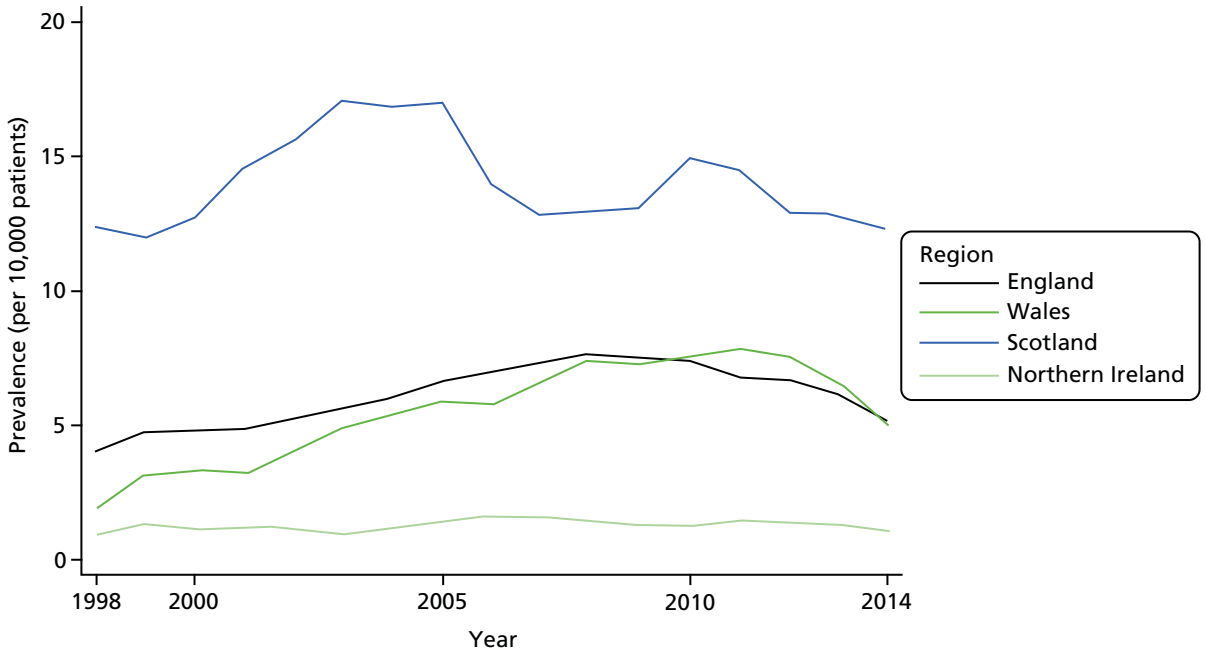

FIGURE 3 Prevalence of OST by country and year. All countries except Northern Ireland showed non-linear trends in the prevalence of OST by year. The non-linearity reflected an increasing trend in the earlier years followed by a decline in the prevalence. The timing of the decline varied by country and may have started earliest in Scotland, followed by England, with Wales showing the latest downturn. Northern Ireland showed a constant prevalence of OST for each year studied.

Trends in patient characteristics

The average age of OST patients increased by 10 years during the study (*Table 3*). About half of this increase was attributable to an ageing sample of patients receiving prolonged OST over many episodes. There was little evidence that the gender ratio varied during the study period. However, this concealed a declining trend in the ratio for the under-30-year-olds, with men representing 70% of this group in 1998 compared with 60% in 2014 ($p < 0.0001$).

TABLE 3 Patient characteristics by year

Year	OST patients	Age (years)	Gender (% male)	Medications (% of patients)					
				M	B	D	BD	ZD	PG
1998	1160	32.78	68.10	86.03	8.45	15.00	42.07	10.78	0.60
1999	1707	32.43	67.72	85.82	7.79	15.35	37.26	12.71	0.64
2000	1948	33.04	68.84	83.21	10.22	17.30	37.47	13.86	0.87
2001	2357	33.43	68.22	77.94	18.24	17.95	35.51	12.13	0.93
2002	2805	33.90	67.45	73.16	23.78	16.51	36.72	13.58	1.21
2003	3274	34.16	67.78	71.90	27.09	12.98	34.18	12.16	1.56
2004	3574	34.57	67.04	69.56	30.64	11.58	32.18	11.39	2.52
2005	3783	35.26	66.93	68.89	32.30	11.10	32.88	12.00	2.88
2006	3978	36.25	68.00	69.43	31.57	10.41	33.43	13.70	3.14
2007	4118	37.21	67.53	69.31	30.67	10.13	32.25	12.94	4.15
2008	4276	37.95	67.45	71.02	29.09	9.10	32.16	12.04	4.07

continued

TABLE 3 Patient characteristics by year (*continued*)

Year	OST patients	Age (years)	Gender (% male)	Medications (% of patients)					
				M	B	D	BD	ZD	PG
2009	4188	38.60	66.52	72.11	27.72	8.55	31.45	12.30	4.75
2010	4129	39.42	67.35	73.12	26.64	8.09	30.35	12.62	6.32
2011	3919	40.16	67.44	73.03	25.85	7.76	30.62	12.78	7.76
2012	3681	40.82	67.24	70.99	27.68	7.25	30.05	12.66	9.07
2013	3413	41.47	67.07	69.32	29.62	7.47	28.66	11.10	11.08
2014	2670	42.55	67.45	67.57	30.82	7.68	26.89	10.90	12.70
Overall	12,780	36.04	66.63	78.62	36.03	15.37	47.44	25.37	9.20
Trend[a]		0.681	0.997	0.971	1.036	0.930	0.971	0.995	1.213
SE (trend)		0.0099	0.0021	0.0023	0.0025	0.0032	0.0021	0.0030	0.0058
p-value		< 0.0001	0.2119	< 0.0001	< 0.0001	< 0.0001	< 0.0001	0.1149	< 0.0001
Deviation		< 0.0001	0.9956	< 0.0001	< 0.0001	< 0.0001	0.0790	0.0070	0.3984

B, buprenorphine; BD, benzodiazepines; D, dihydrocodeine; M, methadone; PG, pregabalin/gabapentin; SE, standard error; ZD, z-drugs.
a Trend is additive for age and multiplicative for all other outcomes.
Note
The totals of the percentages exceed 100% as a result of some patients being prescribed multiple medications within any given year.

During the study, the use of methadone, dihydrocodeine and benzodiazepines was decreasing while the use of buprenorphine and gabapentinoids was increasing (*Figure 4*). Deviations from linearity for methadone and buprenorphine suggested that the major changes occurred up to 2006, with less evidence of any changes after that date. Although there was evidence of a declining prevalence for the prescription of z-drugs, the effect size was small, reflecting a prevalence among OST patients of ≈12. Considering the prevalence of any of these three medications, the prevalence was declining up to 2002 but with no strong evidence of any change after that year. Overall, 78.6% [95% confidence interval (CI) 77.9% to 79.3%], 36.0% (95% CI 35.2% to 36.9%), 15.4% (95% CI 14.7% to 16.0%), 47.4% (95% CI 46.6% to 48.3%), 25.4% (95% CI 24.6% to 28.1%) and 9.2% (95% CI 6.7% to 9.7%) of patients were prescribed methadone, buprenorphine, dihydrocodeine, benzodiazepines, z-drugs or gabapentinoids, respectively.

Trends in episode characteristics

Overall, average dose increased during the study, although there was evidence that this trend may have changed after 2008 (*Table 4*). Linear trends after this date showed a decreasing effect, with –1.057 (95% CI –1.123 to –0.966) and –0.151 (95% CI –0.177 to –0.126) for methadone and buprenorphine, respectively. Both medications showed an increasing adherence to guidelines with optimal dose across the whole study. However, the deviation statistics suggested a more complex pattern. After 2008, methadone episodes showed a declining adherence, multiplicative trend (0.96, 95% CI 0.94 to 0.99), whereas buprenorphine showed no trend (1.02, 95% CI 0.99 to 1.06).

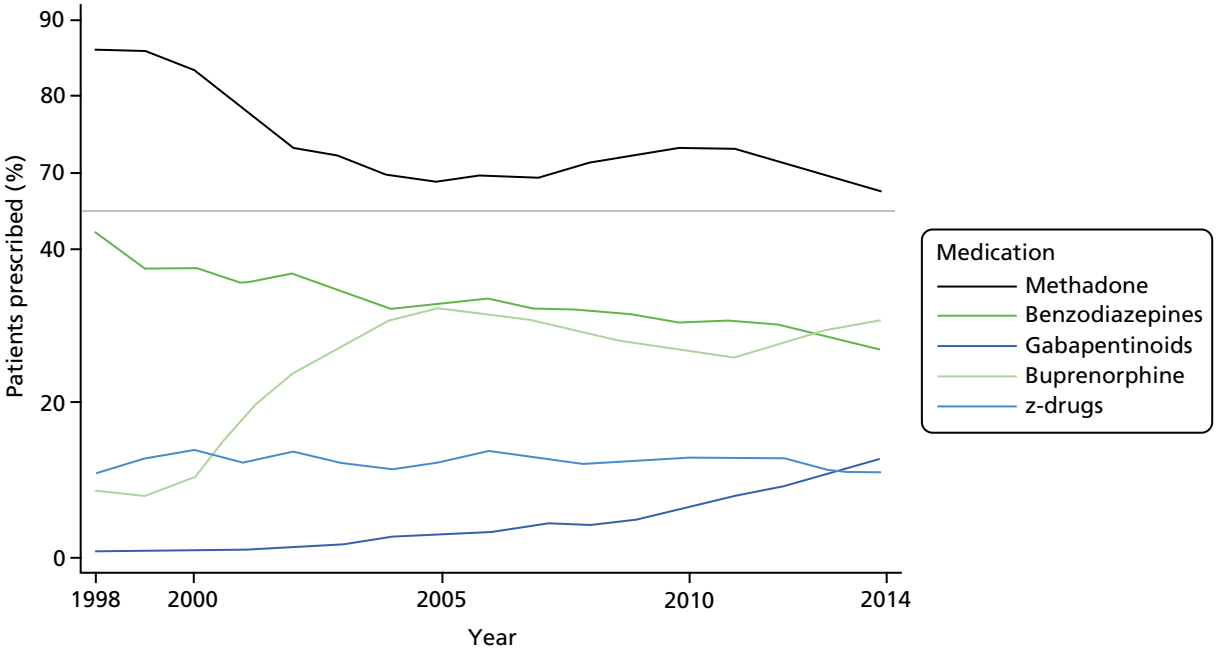

FIGURE 4 Opiate substitution treatment medications, benzodiazepines, z-drugs and gabapentinoids prescribed to OST patients by year. Overall, during the study, prescriptions of methadone declined, whereas those for buprenorphine increased. There may be some evidence to suggest that, after 2007, the percentage of OST patients prescribed these medications remained constant. Benzodiazepines and z-drugs were prescribed to a declining proportion of OST patients as time progressed. Gabapentinoids were increasingly prescribed, from < 1% in 1998 to > 10% in 2014.

The predicted median durations by year are shown in *Table 4*. The mean durations are not reported because of the skewed nature of the distribution. On-treatment duration reached a maximum in 2010 for methadone (*Figure 5*). By contrast, duration for buprenorphine was still increasing by the end of the study. Off-treatment durations were generally increasing throughout the study but there were periods when duration appeared to be constant. For methadone, there was no evidence of any increase before 2009 (HR 1.01, 95% CI 1.00 to 1.02; $p = 0.180$). Similarly, for buprenorphine, during the period 2002–8, off-treatment duration remained constant (HR 1.01, 95% CI 0.99 to 1.03; $p = 0.306$).

The associations of gender, age, comorbidity and region with on- and off-durations are reported in *Table 5*. Age and gender were associated with on-treatment duration for buprenorphine only, with older women tending to have longer durations (lower HR). Those with comorbid chronic illnesses tended to have longer durations for both medications. For off-treatment duration, gender had no association with either medication and comorbidity had no association with buprenorphine. Older patients tended to have longer intervals between treatments. Adjusting for these variables did not markedly change the duration results (*Table 6*).

In a sensitivity analysis, we also analysed duration using the start year of on or off treatment rather than each year associated with an episode. This had two consequences: (1) episodes with on/off treatment starting before the study start date were excluded and (2) an episode contributed to only 1 year however long the period on/off treatment. As a result, it was appropriate to consider each episode as only a single record. Despite these changes to the data, the median durations were very similar (*Table 7*).

TABLE 4 Episode characteristics by methadone or buprenorphine episodes and by year

	Number of episodes			Mean dose (mg)		Optimal dose (%)		On-treatment duration (days)			Off-treatment duration (days)		
Year	M	B	Other	M	B	M	B	M	B	All	M	B	All
1998	1062	97	425	41.95	2.30	25.08	16.67	76	57	82	182	89	163
1999	1366	166	619	40.86	2.47	26.79	8.96	66	36	69	206	74	172
2000	1526	199	842	39.11	2.80	21.45	7.62	58	29	62	177	101	166
2001	1698	351	1146	40.99	3.04	27.39	14.80	77	41	75	179	125	173
2002	1885	579	1323	43.67	4.28	34.72	18.92	80	45	80	182	144	179
2003	2109	776	1406	46.21	5.13	41.59	23.93	100	46	91	172	146	168
2004	2180	885	1506	48.05	5.47	45.36	28.35	98	47	93	196	148	176
2005	2077	998	1609	51.28	6.21	51.01	30.15	122	48	103	204	142	175
2006	2232	1025	1682	53.66	6.46	56.17	25.80	134	48	108	195	142	175
2007	2366	1017	1686	55.71	7.30	60.48	31.40	141	42	102	199	165	181
2008	2560	996	1601	57.00	7.32	63.97	33.89	151	48	110	186	149	169
2009	2507	999	1559	56.30	7.27	62.69	27.91	144	46	102	220	137	179
2010	2497	931	1441	56.83	7.27	61.98	31.19	178	53	122	209	152	181
2011	2376	868	1288	54.82	6.70	63.65	29.57	140	52	107	259	150	197
2012	2145	911	1158	52.50	6.62	62.87	33.45	121	61	99	254	151	197
2013	1928	851	1016	52.20	6.94	59.38	32.67	94	58	82	219	161	185
2014	1405	626	716	52.64	7.17	55.76	36.36	68	62	64	293	198	248

	Number of episodes			Mean dose (mg)		Optimal dose (%)		On-treatment duration (days)			Off-treatment duration (days)		
Year	M	B	Other	M	B	M	B	M	B	All	M	B	All
Overall	17,787	8497	8143	51.66	6.54	48.58	28.49	106	48	93	202	146	179
Trend[a]				0.959	0.198	1.131	1.061	1.048	1.028	1.020	1.023	1.024	1.013
SE (trend)				0.0030	0.0013	0.0036	0.0065	0.0033	0.0047	0.0025	0.0026	0.0039	0.0020
p-value				< 0.0001	< 0.0001	< 0.0001	< 0.0001	< 0.0001	< 0.0001	< 0.0001	< 0.0001	< 0.0001	< 0.0001
Deviation				< 0.0001	< 0.0001	< 0.0001	< 0.0001	< 0.0001	0.0952	< 0.0001	< 0.0001	< 0.0001	0.0002

B, buprenorphine only; M, methadone only; SE, standard error.
a Trend is additive for mean dose and multiplicative for all other outcomes.
Notes
'Other' medication regimes included dihydrocodeine and multiple medications.
Optimal doses are reported as percentage of episodes with ≥ 60 mg methadone or ≥ 12 mg buprenorphine.
Median durations were estimated by parametric survival analysis using a log-normal distribution.

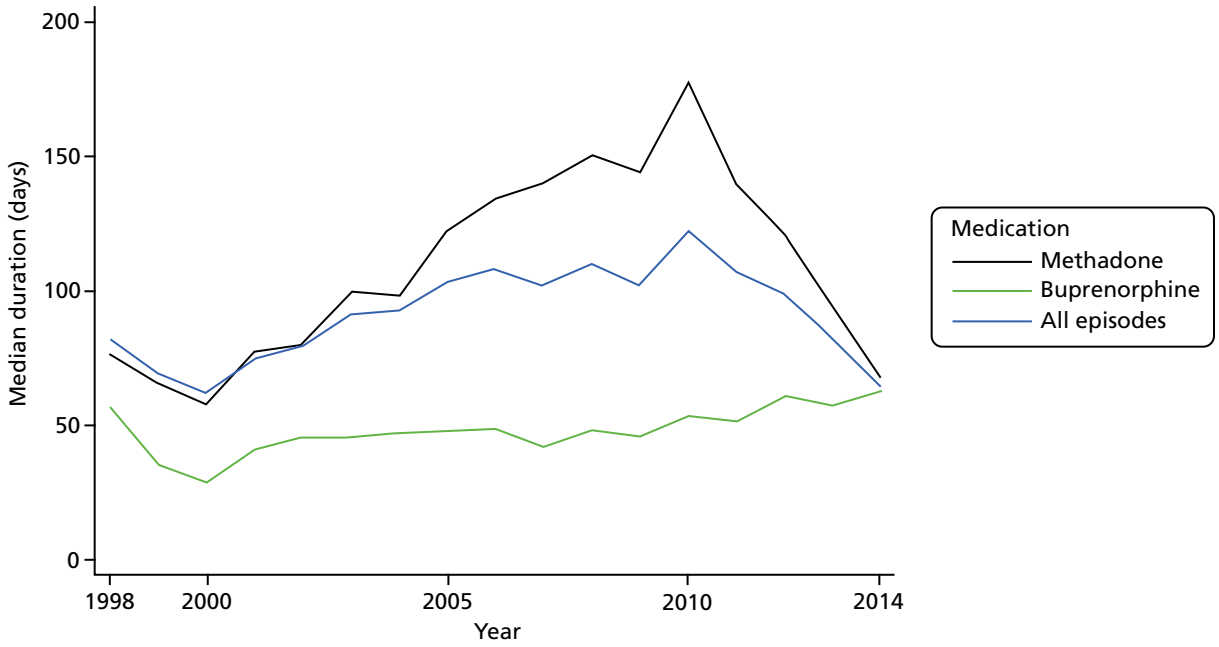

FIGURE 5 Duration of OST by type and year. The median duration of buprenorphine treatment increased overall during the study, although there was some variability in the early years owing to the small number of episodes. Methadone episodes showed an increasing duration up to 2010 but then decreased such that in 2014 their durations were similar to those of buprenorphine.

Summary

Our data suggest that the prevalence of OST has been declining since 2010. Extrapolation to the whole UK suggests that < 50,000 patients are currently being treated in primary care. This number is lower than other estimates[9,11] and may reflect either other patients being treated by alternative services such as community drug agencies or that CPRD practices were not representative of all UK general practices.

Trends in medications suggest that prescribing buprenorphine has become more prevalent, with about 30% of patients in 2014 prescribed this medication. Co-prescription of gabapentinoids was rare at the start of this study but by the end it was prescribed to about 13% of patients. Benzodiazepines were more commonly co-prescribed but the prevalence of this medication among OST patients per year declined, although they were still prescribed to about 26% of patients by the end of the study. The prevalence of co-prescription of z-drugs changed very little during the study.

The mean doses and the proportion of treatment episodes reaching an optimal dose increased up to about 2008, with evidence of declining trends after this date for most outcomes. The exception was optimal dose for buprenorphine for which the evidence suggested a stable proportion post 2008. Shorter treatment duration for buprenorphine than for methadone treatment has also been reported in other studies.[16,21–23,63] Off-treatment durations increased for both methadone and buprenorphine after 2008. It is interesting to note that the shorter on-treatment duration for buprenorphine was associated with a shorter off-treatment duration.

TABLE 5 Effect of confounders for on- and off-treatment duration by OST type

		On treatment				Off treatment			
		Methadone		Buprenorphine		Methadone		Buprenorphine	
Confounder	Category	HR (95% CI)	*p*-value	HR (95% CI)	*p*-value	HR (95% CI)	*p*-value	HR (95% CI)	*p*-value
Gender	Male	0.99 (0.94 to 1.06)	0.8483	1.25 (1.16 to 1.35)	< 0.0001	0.97 (0.93 to 1.02)	0.2704	1.01 (0.96 to 1.08)	0.6385
	Female	1 (reference)		1 (reference)		1 (reference)		1 (reference)	
Age (years)	< 30	1 (reference)	0.2908	1 (reference)	< 0.0001	1 (reference)	< 0.0001	1 (reference)	< 0.0001
	30–39	1.06 (0.99 to 1.14)		1.14 (1.02 to 1.27)		0.82 (0.77 to 0.86)		0.93 (0.85 to 1.02)	
	40–49	1.05 (0.97 to 1.15)		0.91 (0.81 to 1.02)		0.62 (0.57 to 0.66)		0.61 (0.55 to 0.66)	
	≥ 50	1.10 (0.97 to 1.24)		0.72 (0.65 to 0.81)		0.54 (0.49 to 0.60)		0.42 (0.38 to 0.46)	
Comorbidity score	0	1 (reference)	< 0.0001	1 (reference)	0.0251	1 (reference)	< 0.0001	1 (reference)	0.2837
	1	1.01 (0.94 to 1.08)		0.98 (0.90 to 1.06)		0.91 (0.86 to 0.96)		0.98 (0.92 to 1.05)	
	≥ 2	0.64 (0.57 to 0.73)		0.84 (0.74 to 0.95)		0.76 (0.69 to 0.85)		1.07 (0.97 to 1.18)	
Region	North East	1.29 (1.00 to 1.66)	< 0.0001	1.38 (1.11 to 1.70)	< 0.0001	1.21 (0.98 to 1.48)	< 0.0001	0.79 (0.67 to 0.92)	< 0.0001
	North West	1 (reference)		1 (reference)		1 (reference)		1 (reference)	
	Yorkshire and the Humber	1.85 (1.61 to 2.14)		1.89 (1.53 to 2.35)		1.52 (1.34 to 1.71)		1.08 (0.91 to 1.29)	
	East Midlands	1.32 (1.13 to 1.53)		1.33 (1.12 to 1.58)		1.40 (1.24 to 1.59)		0.95 (0.83 to 1.09)	
	West Midlands	1.80 (1.62 to 2.01)		1.12 (0.98 to 1.28)		1.72 (1.57 to 1.88)		1.13 (1.02 to 1.26)	
	East	1.45 (1.29 to 1.62)		1.27 (1.09 to 1.48)		1.49 (1.36 to 1.63)		1.17 (1.04 to 1.32)	

continued

TABLE 5 Effect of confounders for on- and off-treatment duration by OST type (*continued*)

		On treatment				Off treatment			
		Methadone		Buprenorphine		Methadone		Buprenorphine	
Confounder	Category	HR (95% CI)	*p*-value	HR (95% CI)	*p*-value	HR (95% CI)	*p*-value	HR (95% CI)	*p*-value
	South West	1.88 (1.68 to 2.10)		1.22 (1.06 to 1.41)		1.72 (1.56 to 1.89)		1.06 (0.95 to 1.18)	
	South Central	2.31 (2.05 to 2.61)		1.16 (1.01 to 1.32)		1.63 (1.48 to 1.80)		1.08 (0.97 to 1.20)	
	London	2.30 (2.03 to 2.62)		1.19 (1.03 to 1.39)		1.46 (1.32 to 1.62)		0.89 (0.80 to 1.00)	
	South East	1.12 (0.95 to 1.33)		1.03 (0.86 to 1.22)		1.90 (1.66 to 2.18)		1.11 (0.97 to 1.27)	
	Northern Ireland	1.62 (0.83 to 3.16)		1.38 (0.99 to 1.90)		2.13 (1.20 to 3.79)		0.61 (0.48 to 0.78)	
	Scotland	3.37 (3.10 to 3.66)		1.12 (0.92 to 1.37)		1.45 (1.35 to 1.55)		1.24 (1.05 to 1.46)	
	Wales	1.98 (1.71 to 2.29)		1.79 (1.52 to 2.09)		2.27 (2.01 to 2.57)		1.28 (1.12 to 1.45)	

All effects are mutually adjusted and adjusted for year.
On treatment: interactions with OST type: $p < 0.0001$ (gender), $p < 0.0001$ (age), $p = 0.0107$ (comorbidity) and $p < 0.0001$ (region).
Off treatment: interactions with OST type: $p = 0.3127$ (gender), $p < 0.0001$ (age), $p < 0.0001$ (comorbidity) and $p < 0.0001$ (region).

TABLE 6 Median episode duration by year and type of medication adjusted for four confounders

	On-treatment duration (days)			Off-treatment duration (days)		
Year	Methadone (only)	Buprenorphine (only)	All[a]	Methadone (only)	Buprenorphine (only)	All[a]
1998	93	73	87	170	126	150
1999	81	43	75	194	98	160
2000	71	33	68	175	126	158
2001	87	43	79	175	132	163
2002	87	46	81	178	140	168
2003	104	46	91	169	135	158
2004	106	48	95	193	139	167
2005	137	49	110	204	137	171
2006	158	49	120	201	139	177
2007	162	43	113	211	164	189
2008	171	51	122	197	155	180
2009	158	51	115	232	148	194
2010	189	59	136	218	165	200
2011	153	59	124	284	171	228
2012	137	67	114	279	164	224
2013	102	64	93	250	176	217
2014	67	70	70	327	216	288
Overall	120	51	101	206	151	184
Trend[b]	1.041	1.034	1.028	1.034	1.030	1.031
SE (trend)	0.0034	0.0049	0.0026	0.0027	0.0038	0.0020
p-value	< 0.0001	< 0.0001	< 0.0001	< 0.0001	< 0.0001	< 0.0001
Deviation	< 0.0001	0.0355	< 0.0001	< 0.0001	0.2703	< 0.0001

SE, standard error.
a All types and combinations of medications.
b Trend is multiplicative for all other outcomes.

Notes
Median durations were estimated by parametric survival analysis using a log-normal distribution. Adjusted for patient age, gender and comorbidity and UK region. Interaction of year with type: $p < 0.0001$ (on treatment), $p = 0.0178$ (off treatment).

TABLE 7 Median episode duration by start year and type of medication

	On-treatment duration (days)			Off-treatment duration (days)		
Year	Methadone (only)	Buprenorphine (only)	All[a]	Methadone (only)	Buprenorphine (only)	All[a]
1998	72	65	78	208	81	180
1999	63	36	67	193	83	169
2000	63	28	67	174	97	164
2001	75	41	73	175	142	174
2002	85	47	85	186	152	182
2003	105	46	96	178	140	169
2004	100	48	94	206	150	180
2005	132	47	108	190	145	171
2006	143	50	110	192	138	169
2007	142	44	104	200	164	180
2008	149	49	110	185	145	166
2009	139	47	99	217	134	177
2010	168	51	115	221	159	187
2011	130	52	102	264	147	198
2012	121	61	97	257	159	203
2013	85	57	77	226	163	192
2014	73	58	69	362	199	279
Overall	106	48	93	203	146	180
Trend[b]	1.0470	1.0240	1.0186	1.0240	1.0225	1.0129
SE (trend)	0.0033	0.0048	0.0026	0.0027	0.0039	0.0020
p-value	< 0.0001	< 0.0001	< 0.0001	< 0.0001	< 0.0001	< 0.0001
Deviation	< 0.0001	0.0480	< 0.0001	< 0.0001	< 0.0001	< 0.0001

SE, standard error.
a All types and combinations of medications.
b Trend is multiplicative for all other outcomes.
Note
Interaction of year with type: $p < 0.0001$ (on and off treatment).

Chapter 5 Comparison of methadone and buprenorphine use in opiate substitution treatment

As seen in the previous chapter, there has been an increase in the use of buprenorphine as part of OST. This chapter, on WP 2, presents the results comparing buprenorphine and methadone on mortality. The main report is published in Hickman *et al.*[61] Reproduced from Hickman *et al.*[61] This is an Open Access article distributed in accordance with the terms of the Creative Commons Attribution (CC BY 4.0) license, which permits others to distribute, remix, adapt and build upon this work, for commercial use, provided the original work is properly cited. See: http://creativecommons.org/licenses/by/4.0/. The text below includes minor additions and formatting changes to the original text.

Aims and objectives

Our main aim was to explore the differences in mortality risk between methadone and buprenorphine and whether or not any effects were modified by treatment period. Our secondary aim was to explore other interactions that may influence the risk of mortality.

Data set for main analyses

There were 26,546 OST episodes involving solely methadone or buprenorphine relating to 11,033 patients. For simplicity in comparing these medications, treatment episodes involving both medications or dihydrocodeine were excluded. In 30,410 person-years of follow-up there were 587 ACM deaths.

Statistical methods

Poisson regression was the main analytic method. In addition to standard adjusted analyses, three methods, more robust to residual confounding were described in the paper: IPW, IV and PSM. Further details are provided below on the IV and PSM analyses.

Sensitivity analyses were performed:

1. Restricting to patients without any evidence of comorbid illnesses. This was to explore whether or not chronic illnesses may have introduced residual confounding, perhaps via palliative care.
2. Including partial episodes involving methadone or buprenorphine. Main analyses involved only episodes involving a single medication to avoid any possible combined effect of multiple medications during an episode. Including episodes with multiple medications allowed a more continuous follow-up of patients, increasing person-years by 19% and the number of deaths by 12%.
3. Additionally adjusting for the tapering of dose during the last 28 days of treatment. Tapering may indicate a planned discharge from treatment rather than poor treatment retention.
4. Using negative binomial regression to take account of possible overdispersion in Poisson regression.
5. Using linear regression and survival analysis to compare the results for risk differences and HRs with IRRs.
6. Using multilevel models to explore whether other sources of variability, in particular between patients, modify the interpretation of results.
7. Analysing only the first or last episode for each patient to investigate whether there was a cumulative effect of multiple episodes.
8. Redefining OST episodes based on a 7-day or 56-day gap instead of the 28-day gap used in main analyses.

Items 1–4 were included in the published paper, although additional background results are included in *Tables 8–11*. Items 5–8 were not included in the published paper but are included now for completeness.

Propensity score matching

As well as IPW, propensity scores were also used to match buprenorphine episodes to methadone episodes using the nearest neighbour procedure. Matching was successful if the difference in logit (propensity score) was ≤ 0.25 SD.[46] For our data, the SD of the logit was 1.28, suggesting a criterion of 0.32. Owing to the limited pool of methadone episodes, it was not always possible to match every buprenorphine episode to a methadone episode using this criterion.

Matching reduced the data to 13,940 (53% of total) and 8938 (57%) episodes for ACM and DRP, respectively. The results from Poisson regressions are shown in *Table 8*. Adjusted results are similar to unadjusted results, suggesting that matching had reduced observed confounding below any level of practical significance.

TABLE 8 Poisson analyses of OST type and period on mortality using matched episodes

		Unadjusted		Adjusted[a]	
Period	OST type	IRR (95% CI)	*p*-value	IRR (95% CI)	*p*-value
All-cause mortality					
On 1–4 weeks		3.02 (2.06 to 4.44)	**< 0.0001**	2.77 (1.88 to 4.09)	**< 0.0001**
On rest		1 (reference)		1 (reference)	
Off 1–4 weeks		10.22 (7.95 to 13.13)		10.09 (7.80 to 13.06)	
Off rest		2.03 (1.59 to 2.60)		2.60 (2.02 to 3.35)	
On 1–4 weeks	Methadone	1 (reference)	**0.0003**	1 (reference)	**0.0031**
	Buprenorphine	0.07 (0.02 to 0.29)	0.0003	0.07 (0.02 to 0.29)	0.0002
On rest (reference)	Methadone	1 (reference)		1 (reference)	
	Buprenorphine	0.36 (0.22 to 0.59)	< 0.0001	0.28 (0.17 to 0.46)	< 0.0001
Off 1–4 weeks	Methadone	1 (reference)		1 (reference)	
	Buprenorphine	0.10 (0.06 to 0.19)	< 0.0001	0.09 (0.05 to 0.16)	< 0.0001
Off rest	Methadone	1 (reference)		1 (reference)	
	Buprenorphine	0.39 (0.26 to 0.56)	< 0.0001	0.27 (0.18 to 0.39)	< 0.0001
Drug-related mortality					
On 1–4 weeks		1.28 (0.30 to 5.53)	**< 0.0001**	1.30 (0.30 to 5.68)	**< 0.0001**
On rest		1 (reference)		1 (reference)	
Off 1–4 weeks		7.36 (3.58 to 15.16)		7.62 (3.63 to 16.01)	
Off rest		2.52 (1.35 to 4.69)		2.61 (1.38 to 4.96)	
On 1–4 weeks	Methadone	1 (reference)	**0.1391**	1 (reference)	**0.1186**
	Buprenorphine		n/e		n/e
On rest (reference)	Methadone	1 (reference)		1 (reference)	
	Buprenorphine	0.61 (0.20 to 1.87)	0.3893	0.54 (0.17 to 1.65)	0.2781
Off 1–4 weeks	Methadone	1 (reference)		1 (reference)	
	Buprenorphine	1.46 (0.48 to 4.46)	0.5078	1.42 (0.46 to 4.35)	0.5382
Off rest	Methadone	1 (reference)		1 (reference)	
	Buprenorphine	0.34 (0.13 to 0.85)	0.0206	0.31 (0.12 to 0.78)	0.0130

n/e, not estimated because there were zero deaths.
a Adjusted for gender, age, year, comorbidity, region and, where applicable, treatment period and OST type.
Notes
Based on 13,940 or 8938 matched episodes (410 all-cause or 56 drug-related deaths).
Main effect and interaction *p*-values (2 or 3 df) are shown in bold.

A comparison of PSM results with confounder and IPW adjusted results in the main paper[61] showed similar effects in terms of the point estimates. However, the CIs for PSM results were wider.

Owing to the reduced number of data for these analyses, for DRP, the full interaction between period and type could not be estimated because there were zero deaths observed for buprenorphine treatment in the first 4 weeks. Estimates of the partial interaction (with 2 df instead of 3 df) were obtained by excluding all data for buprenorphine in the first 4 weeks of treatment.

Instrumental variable analysis

We explored the usefulness of a GP's previous prescription as an IV.[58,59] Because a treatment episode typically involved many prescriptions, we concentrated on the initiation of treatment as the critical time when the choice of medication was made. There were 3409 GPs associated with prescribing methadone or buprenorphine at this time. Their histories of treatment initiation covered 26,546 episodes, with an additional 728 episodes predating the study period (*Figure 6*). Because the time of day was unavailable for prescriptions within CPRD, 4560 episodes (13%) initiated on the same day by the same GP were assigned a random generation sequence. There were sufficient histories to provide information on the previous prescription for 2213 GPs (65%).

The majority of GPs tended to have a history of prescribing only one type of medication at the initiation of treatment, with 1269 (37%) prescribing methadone and 959 (28%) prescribing buprenorphine. However, these GPs were generally associated with shorter histories such that these 65% of GPs accounted for only 8606 (25%) episodes. These GPs were excluded from the IV analyses.

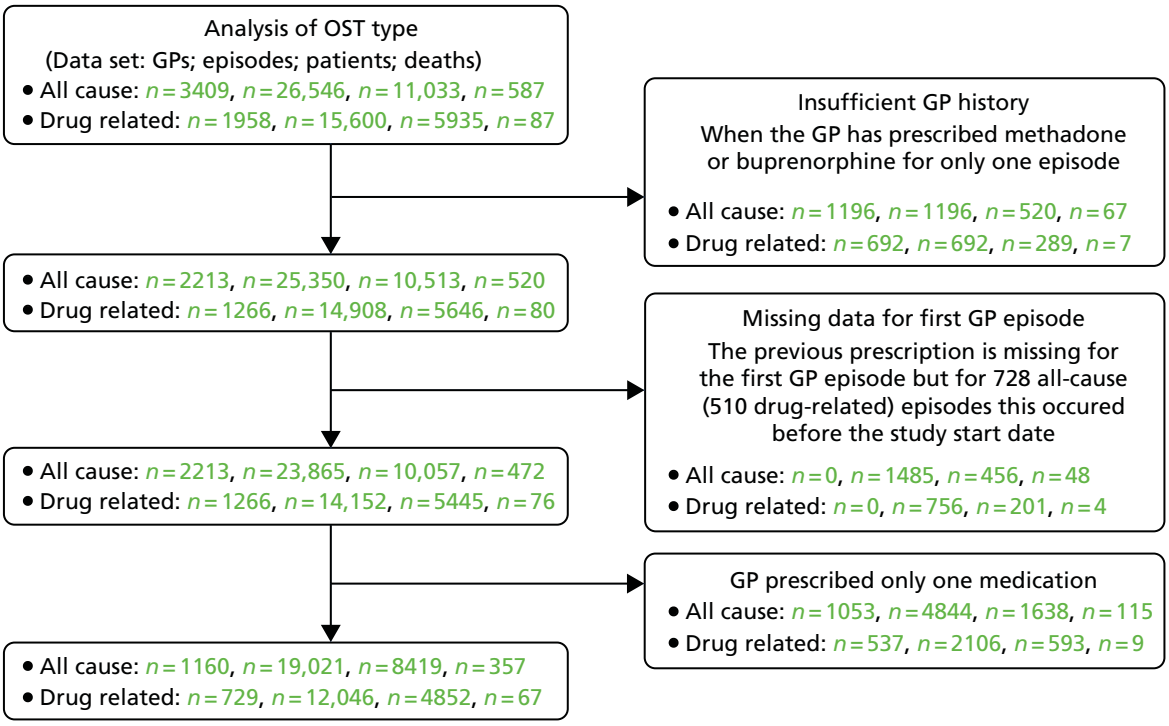

FIGURE 6 Flow chart of data available for IV analyses. The previous GP prescription was used as an IV. About 35% of GPs had initiated an OST episode on only one occasion and so were excluded from the analyses. For 33–40% of GPs, data were available before the study start date. Hence, the number of available episodes did not reduce by the number of GPs. GPs who prescribed only one medication, either methadone or buprenorphine, were also excluded as the IV would be equivalent to the prescribed medication and its associated confounding.

Using the previous prescription as an IV reduced the sample to 8419 patients, 19,021 episodes and 357 deaths in ACM analyses, and 4852 patients, 12,046 episodes and 67 deaths in DRP analyses. The proportions of buprenorphine episodes, 34%, remained similar to the 35% for current prescriptions. By contrast, the proportion of those episodes associated with deaths, 31%, doubled from the 14% with current prescriptions.

An investigation of the criteria for a valid IV showed strong associations between the choice of prescribed medication and IVs. Agreement occurred in 71% of episodes for ACM and in 70% of episodes for DRP. However, the IV remained associated with confounders with an R^2 of 10.5% and 6.1% for ACM and DRP, respectively. These associations were similar to those observed between OST type and confounders (*Table 9a*). These results suggested that previous prescription would act as a poor IV. Similar conclusions were reached when regression coefficients were compared (*Table 9b*).

Confounding

In the main report, confounding was assessed using unadjusted associations of predictors (in the propensity score model) with OST type. Comparing the predicted probabilities of being prescribed buprenorphine, the differences between categories for each predictor were reduced in IPW and PSM models compared with an unadjusted model (see table S2 in Hickman *et al.*[61]). For instance, the differences between men and women in being prescribed buprenorphine reduced from 7% in an unadjusted model to 0.5% in the IPW model. In *Table 9*, we extend these analyses to report the multivariable associations between OST type and all confounders. These analyses were based on linear regressions between OST type (or the IV acting as a proxy for OST type) and confounders using the weights implicit in the Poisson regressions on mortality. Comparisons were made with the standard covariate adjusted model. In part (a), R^2 statistics are reported for individual confounders and overall. In part (b), the regression coefficients for the multivariable models

TABLE 9a Degree of confounding and matching for OST type by analysis type: summary of associations

	Type of analysis			
Confounding[a]	Adjusted	IPW	PSM	IV
Gender	0.33	0.01	0.05	0.19
Age	5.64	0.04	0.17	4.45
Year	0.01	0.69	1.21	0.63
Comorbidity score	2.90	0.52	0.79	2.27
Region	5.75	1.72	1.53	6.47
All	11.38	3.16	3.60	10.52
Matching[b]	1.27	0.17	0.01	1.22
n (episodes)	26,546	26,546	13,940	19,021
n (patients)	11,033	11,033	5921	7582
n (deaths)	587	587	410	357

a Degree of confounder was assessed by R^2 (%) from linear regressions of OST type on all five confounders. Independent contributions of each confounder are also reported.
b Matching was assessed by linear regressions of OST type on logit(propensity score). When the IV (previous prescription by the GP) was for a different medication from the current prescription, the logit was negated. The results reflect the estimated effect of difference between OST types (buprenorphine minus methadone).

TABLE 9b Degree of confounding and matching for OST type by analysis type: effect sizes from multiple linear regressions of OST type on confounders

Variable	Category	Type of analysis			
		Adjusted	IPW	PSM	IV
Gender	Male	–0.017	0.008	0.005	–0.016
	Female	0 (reference)			
Age (years)	< 30	0 (reference)			
	30–39	0.018	0.023	0.014	–0.010
	40–49	0.059	0.042	0.054	0.011
	≥ 50	0.162	0.001	0.014	0.145
Year	1998–9	0 (reference)			
	2000–4	0.002	–0.103	–0.149	0.018
	2005–9	–0.015	–0.133	–0.183	0.093
	2010–14	–0.029	–0.140	–0.190	0.062
Comorbidity score	0	0 (reference)			
	1	–0.004	–0.010	0.001	0.001
	≥ 2	0.057	0.068	0.080	0.066
Region	North East	0.362	0.159	0.160	0.336
	North West	0 (reference)			
	Yorkshire and the Humber	0.110	0.029	0.035	0.064
	East Midlands	0.146	0.066	0.086	0.181
	West Midlands	0.089	–0.005	–0.006	0.063
	East	0.052	0.009	0.017	0.050
	South West	0.006	–0.045	–0.044	0.079
	South Central	0.130	0.026	0.029	0.127
	London	–0.028	–0.052	–0.064	–0.043
	South East	0.096	–0.001	0.074	0.093
	Northern Ireland	0.045	–0.140	–0.167	0.097
	Scotland	–0.053	–0.041	0.011	–0.180
	Wales	0.081	–0.039	–0.005	0.146
R^2 (%)		11.38	3.16	3.60	10.52

Note
Effect sizes reflect differences in the propensity to receive buprenorphine.

are reported. Both PSM and IPW reduced the associations with observed confounders, although the association with calendar year increased.

A comparison of confounder associations with mortality showed that all variables were associated with either ACM or DRP. Gender had a stronger association with DRP, whereas age and region had a stronger association with ACM (*Table 10*).

TABLE 10 Mutually adjusted associations of confounders with mortality

		All-cause mortality		Drug-related mortality	
Confounder	Category	IRR (95% CI)	*p*-value	IRR (95% CI)	*p*-value
Gender	Male	1.13 (0.95 to 1.34)	0.1769	4.08 (2.04 to 8.15)	0.0001
	Female	1 (reference)		1 (reference)	
Age (years)	< 30	1 (reference)	< 0.0001	1 (reference)	0.5135
	30–39	1.20 (0.85 to 1.71)		1.12 (0.62 to 2.02)	
	40–49	2.06 (1.45 to 2.92)		0.89 (0.44 to 1.79)	
	≥ 50	3.27 (2.31 to 4.65)		0.65 (0.28 to 1.54)	
Year	1998–9	1 (reference)	0.0028	1 (reference)	0.0210
	2000–4	0.72 (0.50 to 1.03)		0.40 (0.20 to 0.82)	
	2005–9	0.65 (0.46 to 0.93)		0.33 (0.16 to 0.68)	
	2010–14	0.54 (0.37 to 0.77)		0.37 (0.18 to 0.79)	
Comorbidity score	0	1 (reference)	< 0.0001	1 (reference)	0.0007
	1	1.39 (1.08 to 1.79)		1.50 (0.92 to 2.46)	
	≥ 2	11.68 (9.48 to 14.40)		3.85 (1.90 to 7.81)	
Region	North East	1.03 (0.53 to 2.01)	0.0003	n/e	0.2529
	North West	1 (reference)		1 (reference)	
	Yorkshire and the Humber	1.64 (1.07 to 2.53)		0.25 (0.03 to 1.81)	
	East Midlands	1.69 (1.10 to 2.61)		0.87 (0.26 to 2.90)	
	West Midlands	0.92 (0.62 to 1.35)		0.60 (0.28 to 1.25)	
	East	1.88 (1.36 to 2.61)		1.46 (0.75 to 2.84)	
	South West	1.08 (0.74 to 1.59)		0.91 (0.46 to 1.77)	
	South Central	0.93 (0.63 to 1.38)		0.44 (0.17 to 1.15)	
	London	1.31 (0.92 to 1.87)		0.93 (0.43 to 2.00)	
	South East	1.50 (0.95 to 2.38)		1.43 (0.59 to 3.49)	
	Northern Ireland	0.53 (0.13 to 2.17)		n/a	
	Scotland	1.39 (1.03 to 1.87)		n/a	
	Wales	0.95 (0.63 to 1.43)		n/a	

n/a, data not available; n/e, not estimated as effect assumed to be same as for North West.

Key findings from the published paper

The overall mortality rates for ACM and DRP were 1.93 and 0.53 per 100 person-years, respectively. DRP was elevated in the first 4 weeks of treatment (IRR 1.93, 95% CI 0.97 to 3.82), the first 4 weeks after treatment ceased (IRR 8.15, 95% CI 5.45 to 12.19) and the remainder of time out of treatment (IRR 2.13, 95% CI 1.47 to 3.09), compared with mortality risk from 4 weeks to the end of treatment. Similar patterns of elevated risks by period were also observed for ACM, although the tendency was for higher IRRs than for DRP (first 4 weeks of treatment, IRR 2.98, 95% CI 2.44 to 3.64; first 4 weeks after treatment ceased, IRR 10.40, 95% CI 9.07 to 11.92; and the remainder of time out of treatment, IRR 2.77, 95% CI 2.42 to 3.17).

Patients on buprenorphine had lower ACM rates in each treatment period than those on methadone, with the strongest beneficial effect being associated with the first 4 weeks of treatment (IRR 0.04, 95% CI 0.01 to 0.15). After IPW adjustment, there was evidence of a lower DRP risk for patients on buprenorphine than for those on methadone at treatment initiation (IRR 0.08, 95% CI 0.01 to 0.48) and for the rest of time on treatment (IRR 0.37, 95% CI 0.17 to 0.79). Model estimates suggested that there was a low probability that methadone or buprenorphine reduced the number of DRPs in the population: 28% and 21%, respectively.

There was evidence that age and comorbidity interacted with OST type ($p < 0.0024$) such that buprenorphine may have lower ACM and DRP risks in older and more comorbid patients.

Sensitivity analyses did not change the conclusions (see table S4 in Hickman *et al.*[61]).

Other sensitivity analyses not reported in published paper

An analysis of risk differences involved linear regression on the mortality rate associated with each record in the data file. The length of time associated with each record was used as a weight in the analysis. These analyses might provide an alternative description of risks to IRRs. Although the ordinal properties of these results matched those from Poisson regression (e.g. the treatment period with the lowest risk was on treatment after the first 4 weeks, and the highest was off treatment in the first 4 weeks), there were power issues for the treatment period effect for DRP (*Table 11*). This possibly reflected the low mortality rate for the reference period in DRP, producing a smaller range of differences in the linear regressions but a larger range in the ratios for the Poisson regressions.

TABLE 11 Linear regression analyses of OST type and period on mortality

		Unadjusted		Adjusted[a]	
Period	OST type	RD (95% CI)	*p*-value	RD (95% CI)	*p*-value
All-cause mortality					
On 1–4 weeks		2.13 (–0.03 to 4.30)	**< 0.0001**	2.31 (0.13 to 4.50)	**< 0.0001**
On rest		0 (reference)		0 (reference)	
Off 1–4 weeks		8.56 (6.50 to 10.61)		8.70 (6.62 to 10.78)	
Off rest		1.21 (0.15 to 2.26)		1.67 (0.58 to 2.76)	
On 1–4 weeks	Methadone	0 (reference)	**< 0.0001**	0 (reference)	**< 0.0001**
	Buprenorphine	–4.05 (–8.47 to 0.38)	0.0734	–5.95 (–10.41 to –1.50)	0.0088
On rest (reference)	Methadone	0 (reference)		0 (reference)	
	Buprenorphine	–0.46 (–1.98 to 1.06)	0.5513	–2.11 (–3.70 to –0.52)	0.0093
Off 1–4 weeks	Methadone	0 (reference)		0 (reference)	
	Buprenorphine	–11.40 (–15.47 to –7.34)	< 0.0001	–13.63 (–17.73 to –9.53)	< 0.0001
Off rest	Methadone	0 (reference)		0 (reference)	
	Buprenorphine	–1.05 (–2.91 to 0.80)	0.2667	–2.95 (–4.86 to –1.05)	0.0024

continued

TABLE 11 Linear regression analyses of OST type and period on mortality (*continued*)

		Unadjusted		Adjusted[a]	
Period	OST type	RD (95% CI)	*p*-value	RD (95% CI)	*p*-value
Drug-related mortality					
On 1–4 weeks		0.60 (–0.76 to 1.95)	**0.1327**	0.61 (–0.76 to 1.98)	**0.1387**
On rest		0 (reference)		0 (reference)	
Off 1–4 weeks		1.43 (0.16 to 2.69)		1.45 (0.17 to 2.73)	
Off rest		0.35 (–0.32 to 1.02)		0.36 (–0.34 to 1.05)	
On 1–4 weeks	Methadone	0 (reference)	**0.8816**	0 (reference)	**0.8928**
	Buprenorphine	–0.94 (–3.62 to 1.73)	0.4891	–0.87 (–3.56 to 1.81)	0.5242
On rest (reference)	Methadone	0 (reference)		0 (reference)	
	Buprenorphine	–0.15 (–1.09 to 0.79)	0.7487	–0.16 (–1.12 to 0.80)	0.7438
Off 1–4 weeks	Methadone	0 (reference)		0 (reference)	
	Buprenorphine	0.27 (–2.16 to 2.71)	0.8252	0.36 (–2.10 to 2.82)	0.7742
Off rest	Methadone	0 (reference)		0 (reference)	
	Buprenorphine	–0.51 (–1.62 to 0.61)	0.3704	–0.46 (–1.60 to 0.68)	0.4281

RD, risk difference (deaths/100 person-years).
a Adjusted for gender, age, year, comorbidity, region and, where applicable, treatment period and OST type.
Note
Main effect and interaction *p*-values (3 df) are shown in bold.

We also more formally took account of the effect of the censoring of follow-up by performing survival analysis instead of Poisson regression (*Table 12*). Right-censoring occurred when patients left a CPRD primary care practice, or if treatment episodes extended beyond the study end or CPRD's last data collection dates. The results of this analysis were very similar to the adjusted Poisson results.

TABLE 12 Proportional hazard survival analyses of OST type and period on mortality

		Unadjusted		Adjusted[a]	
Period	OST type	HR (95% CI)	*p*-value	HR (95% CI)	*p*-value
All-cause mortality					
On 1–4 weeks		3.05 (2.21 to 4.20)	**< 0.0001**	3.06 (2.21 to 4.25)	**< 0.0001**
On rest		1 (reference)		1 (reference)	
Off 1–4 weeks		8.62 (6.96 to 10.68)		9.49 (7.59 to 11.86)	
Off rest		2.44 (1.99 to 3.00)		2.79 (2.26 to 3.44)	
On 1–4 weeks	Methadone	1 (reference)	**< 0.0001**	1 (reference)	**0.0002**
	Buprenorphine	0.03 (0.01 to 0.12)	< 0.0001	0.04 (0.01 to 0.15)	< 0.0001
On rest (reference)	Methadone	1 (reference)		1 (reference)	
	Buprenorphine	0.25 (0.16 to 0.39)	< 0.0001	0.25 (0.15 to 0.39)	< 0.0001
Off 1–4 weeks	Methadone	1 (reference)		1 (reference)	
	Buprenorphine	0.05 (0.03 to 0.09)	< 0.0001	0.07 (0.04 to 0.12)	< 0.0001
Off rest	Methadone	1 (reference)		1 (reference)	
	Buprenorphine	0.21 (0.14 to 0.29)	< 0.0001	0.21 (0.15 to 0.30)	< 0.0001

TABLE 12 Proportional hazard survival analyses of OST type and period on mortality (*continued*)

		Unadjusted		Adjusted[a]	
Period	OST type	HR (95% CI)	*p*-value	HR (95% CI)	*p*-value
Drug-related mortality					
On 1–4 weeks		3.09 (1.40 to 6.83)	**< 0.0001**	2.94 (1.32 to 6.59)	**< 0.0001**
On rest		1 (reference)		1 (reference)	
Off 1–4 weeks		6.05 (3.32 to 11.03)		5.98 (3.23 to 11.07)	
Off rest		2.27 (1.36 to 3.78)		2.27 (1.35 to 3.83)	
On 1–4 weeks	Methadone	1 (reference)	**0.1705**	1 (reference)	**0.1552**
	Buprenorphine	0.27 (0.03 to 2.18)	0.2178	0.27 (0.03 to 2.23)	0.2248
On rest (reference)	Methadone	1 (reference)		1 (reference)	
	Buprenorphine	0.57 (0.20 to 1.66)	0.3064	0.57 (0.19 to 1.65)	0.2973
Off 1–4 weeks	Methadone	1 (reference)		1 (reference)	
	Buprenorphine	1.49 (0.58 to 3.87)	0.4101	1.62 (0.63 to 4.19)	0.3207
Off rest	Methadone	1 (reference)		1 (reference)	
	Buprenorphine	0.39 (0.16 to 0.96)	0.0403	0.42 (0.17 to 1.04)	0.0613

a Adjusted for gender, age, year, comorbidity, region and, where applicable, treatment period and OST type.
Note
Main effect and interaction *p*-values (3 df) are shown in bold.

We also considered whether or not clustering by patient biased the standard errors (SEs) used in standard analyses. There was some evidence of inflated SEs compared with standard Poisson analyses, but the changes were minor (*Table 13*). These analyses also changed IRR estimates, but, again, the changes were minor.

TABLE 13 Mixed-effects Poisson regression analyses of OST type and period on mortality

		Unadjusted		Adjusted[a]	
Period	OST type	IRR (95% CI)	*p*-value	IRR (95% CI)	*p*-value
All-cause mortality					
On 1–4 weeks		2.60 (1.85 to 3.64)	**< 0.0001**	1.96 (1.37 to 2.80)	**< 0.0001**
On rest		1 (reference)		1 (reference)	
Off 1–4 weeks		10.51 (8.29 to 13.32)		9.42 (7.42 to 11.95)	
Off rest		3.03 (2.35 to 3.91)		3.25 (2.57 to 4.12)	
On 1–4 weeks	Methadone	1 (reference)	**0.0026**	1 (reference)	**0.0022**
	Buprenorphine	0.09 (0.02 to 0.36)	0.0008	0.06 (0.01 to 0.27)	0.0002
On rest (reference)	Methadone	1 (reference)		1 (reference)	
	Buprenorphine	0.44 (0.26 to 0.75)	0.0025	0.27 (0.16 to 0.47)	< 0.0001
Off 1–4 weeks	Methadone	1 (reference)		1 (reference)	
	Buprenorphine	0.14 (0.08 to 0.24)	< 0.0001	0.07 (0.04 to 0.13)	< 0.0001
Off rest	Methadone	1 (reference)		1 (reference)	
	Buprenorphine	0.36 (0.24 to 0.55)	< 0.0001	0.16 (0.10 to 0.25)	< 0.0001

continued

TABLE 13 Mixed-effects Poisson regression analyses of OST type and period on mortality (*continued*)

		Unadjusted		Adjusted[a]	
Period	OST type	IRR (95% CI)	*p*-value	IRR (95% CI)	*p*-value
Drug-related mortality					
On 1–4 weeks		3.21 (1.44 to 7.17)	**< 0.0001**	3.04 (1.31 to 7.06)	**< 0.0001**
On rest		1 (reference)		1 (reference)	
Off 1–4 weeks		6.59 (3.51 to 12.36)		7.05 (3.64 to 13.68)	
Off rest		2.42 (1.40 to 4.20)		2.87 (1.53 to 5.40)	
On 1–4 weeks	Methadone	1 (reference)	**0.2612**	1 (reference)	**0.1687**
	Buprenorphine	0.26 (0.03 to 2.11)	0.2058	0.29 (0.03 to 2.58)	0.2681
On rest (reference)	Methadone	1 (reference)		1 (reference)	
	Buprenorphine	0.58 (0.19 to 1.77)	0.3395	0.69 (0.20 to 2.43)	0.5659
Off 1–4 weeks	Methadone	1 (reference)		1 (reference)	
	Buprenorphine	1.27 (0.47 to 3.38)	0.6369	1.62 (0.56 to 4.72)	0.3776
Off rest	Methadone	1 (reference)		1 (reference)	
	Buprenorphine	0.38 (0.16 to 0.95)	0.0390	0.40 (0.14 to 1.13)	0.0836

a Adjusted for gender, age, year, comorbidity, region and, where applicable, treatment period and OST type.
Note
Main effect and interaction *p*-values (3 df) are shown in bold.

In addition, we analysed subsets of data relating to either the first or the last episode. Any differences between these two sets of results might indicate a cumulative effect of repeated treatment on the risk of death. As the number of episodes increase, the first 4 weeks after treatment may be associated with an increased risk of ACM (*Tables 14* and *15*).

TABLE 14 Poisson analyses of mortality using the last episode for each patient

		Unadjusted		Adjusted[a]	
Period	OST type	IRR (95% CI)	*p*-value	IRR (95% CI)	*p*-value
All-cause mortality					
On 1–4 weeks		4.87 (3.54 to 6.69)	**< 0.0001**	3.98 (2.88 to 5.51)	**< 0.0001**
On rest		1 (reference)		1 (reference)	
Off 1–4 weeks		19.57 (15.84 to 24.18)		17.31 (13.90 to 21.57)	
Off rest		2.82 (2.30 to 3.45)		2.91 (2.36 to 3.59)	
On 1–4 weeks	Methadone	1 (reference)	**0.0021**	1 (reference)	**0.0040**
	Buprenorphine	0.13 (0.03 to 0.52)	0.0041	0.09 (0.02 to 0.37)	0.0008
On rest (reference)	Methadone	1 (reference)		1 (reference)	
	Buprenorphine	0.68 (0.43 to 1.06)	0.0893	0.43 (0.27 to 0.67)	0.0002
Off 1–4 weeks	Methadone	1 (reference)		1 (reference)	
	Buprenorphine	0.24 (0.14 to 0.40)	< 0.0001	0.13 (0.08 to 0.22)	< 0.0001
Off rest	Methadone	1 (reference)		1 (reference)	
	Buprenorphine	0.62 (0.44 to 0.87)	0.0055	0.27 (0.19 to 0.39)	< 0.0001

TABLE 14 Poisson analyses of mortality using the last episode for each patient (*continued*)

Period	OST type	Unadjusted		Adjusted[a]	
		IRR (95% CI)	*p*-value	IRR (95% CI)	*p*-value
Drug-related mortality					
On 1–4 weeks		4.90 (2.23 to 10.79)	**< 0.0001**	4.41 (1.98 to 9.80)	**< 0.0001**
On rest		1 (reference)		1 (reference)	
Off 1–4 weeks		12.22 (6.73 to 22.19)		10.58 (5.72 to 19.57)	
Off rest		2.77 (1.67 to 4.59)		2.44 (1.44 to 4.14)	
On 1–4 weeks	Methadone	1 (reference)	**0.1848**	1 (reference)	**0.1725**
	Buprenorphine	0.32 (0.04 to 2.61)	0.2887	0.35 (0.04 to 2.82)	0.3211
On rest (reference)	Methadone	1 (reference)		1 (reference)	
	Buprenorphine	0.66 (0.23 to 1.90)	0.4407	0.64 (0.22 to 1.86)	0.4089
Off 1–4 weeks	Methadone	1 (reference)		1 (reference)	
	Buprenorphine	1.53 (0.60 to 3.88)	0.3684	1.67 (0.65 to 4.33)	0.2869
Off rest	Methadone	1 (reference)		1 (reference)	
	Buprenorphine	0.40 (0.17 to 0.96)	0.0411	0.43 (0.17 to 1.06)	0.0667

a Adjusted for gender, age, year, comorbidity, region and, where applicable, treatment period and OST type.
Note
Main effect and interaction *p*-values (3 df) are shown in bold.

TABLE 15 Poisson analyses of mortality using the first episode for each patient

Period	OST type	Unadjusted		Adjusted[a]	
		IRR (95% CI)	*p*-value	IRR (95% CI)	*p*-value
All-cause mortality					
On 1–4 weeks		3.94 (2.64 to 5.87)	**< 0.0001**	3.03 (2.01 to 4.56)	**< 0.0001**
On rest		1 (reference)		1 (reference)	
Off 1–4 weeks		12.69 (9.77 to 16.49)		10.66 (8.12 to 14.00)	
Off rest		2.01 (1.54 to 2.60)		2.10 (1.60 to 2.75)	
On 1–4 weeks	Methadone	1 (reference)	**0.0103**	1 (reference)	**0.0473**
	Buprenorphine	0.10 (0.01 to 0.71)	0.0215	0.07 (0.01 to 0.49)	0.0080
On rest (reference)	Methadone	1 (reference)		1 (reference)	
	Buprenorphine	0.55 (0.30 to 0.99)	0.0477	0.29 (0.16 to 0.53)	0.0001
Off 1–4 weeks	Methadone	1 (reference)		1 (reference)	
	Buprenorphine	0.17 (0.08 to 0.37)	< 0.0001	0.09 (0.04 to 0.19)	< 0.0001
Off rest	Methadone	1 (reference)		1 (reference)	
	Buprenorphine	0.66 (0.41 to 1.05)	0.0817	0.26 (0.16 to 0.42)	< 0.0001

continued

TABLE 15 Poisson analyses of mortality using the first episode for each patient (*continued*)

		Unadjusted		Adjusted[a]	
Period	OST type	IRR (95% CI)	*p*-value	IRR (95% CI)	*p*-value
Drug-related mortality					
On 1–4 weeks		4.73 (1.53 to 14.67)	**< 0.0001**	3.90 (1.24 to 12.26)	**< 0.0001**
On rest		1 (reference)		1 (reference)	
Off 1–4 weeks		11.36 (5.01 to 25.75)		8.37 (3.61 to 19.42)	
Off rest		2.69 (1.29 to 5.63)		2.01 (0.94 to 4.31)	
On 1–4 weeks	Methadone	1 (reference)	**0.8840**	1 (reference)	**0.9537**
	Buprenorphine	0.73 (0.08 to 7.02)	0.7852	0.82 (0.08 to 8.06)	0.8679
On rest (reference)	Methadone	1 (reference)		1 (reference)	
	Buprenorphine	1.29 (0.35 to 4.78)	0.6993	1.33 (0.35 to 5.04)	0.6721
Off 1–4 weeks	Methadone	1 (reference)		1 (reference)	
	Buprenorphine	0.73 (0.19 to 2.77)	0.6472	0.90 (0.23 to 3.53)	0.8851
Off rest	Methadone	1 (reference)		1 (reference)	
	Buprenorphine	0.66 (0.21 to 2.02)	0.4635	0.83 (0.26 to 2.63)	0.7479

a Adjusted for gender, age, year, comorbidity, region and, where applicable, treatment period and OST type.
Note
Analyses based on 362 all-cause and 44 drug-related deaths.
Main effect and interaction *p*-values (3 df) are shown in bold.

Finally, we analysed ACM using different gaps in patient prescription histories to indicate a new treatment episode. Decreasing the gap from 28 days in main analyses increased the number of episodes but also increased the number of patients (*Table 16*). This was a result of treatment durations being shortened, thereby increasing the chance that only one medication was prescribed. Conversely, increasing the gap decreased the number of episodes and patients. The interaction effects were relatively robust to changes in the definition of episodes with changes in effect sizes restricted to the treatment period main effect.

Summary

All analyses showed an increased risk of mortality in the first 4 weeks of treatment and the first 4 weeks after treatment ceased, compared with after 4 weeks on treatment. These results are consistent with other reports.[53,64] Overall, mortality rates were higher during off treatment than during on treatment.[30,64–66]

All analyses for ACM and IPW analyses for DRP showed the presence of an interaction with OST type, suggesting that the association in the first 4 weeks of treatments was more pronounced with methadone than with buprenorphine. These results are consistent with a recent Australian study.[53] However, although we found a similar difference in risk for the remainder of time on treatment, that study found no differences between methadone and buprenorphine. Our IRRs comparing buprenorphine with methadone for on- and off-treatment periods are consistent with pooled estimates from a recent systematic review.[64]

The presence of an OST type by period interaction only in IPW for DRP may reflect the reduced power associated with only 87 deaths. Although this may be an indication of under-reporting of DRP in causes of death, the availability of such information for only 50% of patients within CPRD at the time of this study was a major contributory factor to the reduction in power.

TABLE 16 Poisson analyses of ACM with episodes defined with 7- or 56-day prescription gap

		7 days		56 days	
Period	OST type	IRR (95% CI)	*p*-value	IRR (95% CI)	*p*-value
On 1–4 weeks		2.05 (1.53 to 2.74)	**< 0.0001**	3.76 (2.66 to 5.32)	**< 0.0001**
On rest		1 (reference)		1 (reference)	
Off 1–4 weeks		5.87 (4.72 to 7.31)		15.00 (12.06 to 18.66)	
Off rest		2.82 (2.29 to 3.46)		2.86 (2.32 to 3.52)	
On 1–4 weeks	Methadone	1 (reference)	**< 0.0001**	1 (reference)	**0.0029**
	Buprenorphine	0.06 (0.02 to 0.16)	< 0.0001	0.03 (0.00 to 0.21)	0.0005
On rest (reference)	Methadone	1 (reference)		1 (reference)	
	Buprenorphine	0.30 (0.19 to 0.48)	< 0.0001	0.24 (0.15 to 0.38)	< 0.0001
Off 1–4 weeks	Methadone	1 (reference)		1 (reference)	
	Buprenorphine	0.08 (0.05 to 0.13)	< 0.0001	0.08 (0.05 to 0.14)	< 0.0001
Off rest	Methadone	1 (reference)		1 (reference)	
	Buprenorphine	0.23 (0.17 to 0.33)	< 0.0001	0.21 (0.15 to 0.31)	< 0.0001
Episodes; patients; deaths		56,058; 11,590; 617		19,277; 10,706; 573	

Note
Analyses adjusted for gender, age, year, comorbidity, region and, where applicable, treatment period and OST type. Main effect and interaction *p*-values (3 df) are shown in bold. Main analyses were based on > 28-day gap in patient prescription histories, leading to 26,546 episodes, 11,033 patients and 587 deaths.

As previously reported,[15–17,25,53] we found increased mortality risks immediately following the cessation of treatment, but, in comparing different OST types, there were some differences. Whereas our data suggested lower risks for buprenorphine with ACM but not with DRP, by contrast, the Australian study reported a lower risk for methadone with DRP during the first 4 weeks following cessation.[53]

It is likely that the differences during treatment cessation after the first 4 weeks are indicative of residual confounding or confounding by indication. Owing to the half-lives of OST medications, any direct pharmacological effects of either medication are likely to be small.[7] However, there may be indirect effects, such as reduced opioid tolerance, with consequences for any relapse to drug abuse.[36] Whether methadone and buprenorphine treatment differ in these respects is unclear. In addition, one would expect any differences in medication to diminish with time. Although this was observed for ACM, with differences halving compared with the first 4 weeks, such a change was not observed for DRP.

Various sensitivity analyses involving different analysis techniques and different subsets of data did not change these conclusions. Although propensity score and IV methods are well-established techniques, we also explore modifications to the SCCS methods in *Chapter 8*.

It should be noted that we lacked information about patients' illicit drug use during their treatment. It is possible that some patients resorted to this to overcome withdrawal symptoms, potentially increasing mortality. Another limitation was the use of naloxone, which may have reduced overdose deaths.

Chapter 6 Co-prescription of benzodiazepines, z-drugs and gabapentinoids with opiate substitution treatment

In *Chapter 4*, we reported that about 50% of patients received benzodiazepines, z-drugs or gabapentinoids in addition to OST. Given that current treatment guidelines discourage this practice,[34,35] in this chapter on WP 3 we will explore the effects on mortality of co-prescription.

Aims and objectives

Our main aim was to explore the effects of co-prescription on mortality risk. For comparison with a recent study,[31] we also analysed deaths from non-drug related causes in addition to ACM and DRP. Given the strong effects on OST type and treatment period noted in WP 2, we also investigated whether or not the co-prescription effects varied with these OST factors.

Data set for the main analyses

There were 29,540 OST episodes involving methadone or buprenorphine (see *Figure 2*). As our primary aim was not to compare OST medications, we included partial episodes of methadone and buprenorphine to increase the power of comparisons. These episodes related to 12,118 patients, of whom 42% received benzodiazepine co-prescription, 20% received z-drug co-prescription and 8% received gabapentinoid co-prescription. In 36,126 person-years of follow-up there were 657 ACM deaths.

Key findings from the submitted paper

The results for co-prescription of the three medications with OST are summarised in *Table 17*. All co-prescribed medications were related to ACM and DRP such that co-prescription increased the risk of mortality. There was evidence of a dose–response relationship for benzodiazepines with DRP but not with ACM. Only gabapentinoids were associated with an increase in risk of non-drug-related mortality.

TABLE 17 Summary of associations between co-prescription with OST and mortality

	Mortality		
Co-prescribed	All cause	Drug related	Non-drug related
Benzodiazepines	1.16	2.02 (D)	
z-drugs	1.83	3.31	
Gabapentinoids	1.99	1.60	2.15

D, dose-related association. Other associations relate to on/off treatment.
Note
Effect sizes are IRRs. Blank cells indicate no association.

Concurrent prescription of benzodiazepine was associated with an approximate doubling of the duration of methadone treatment (adjusted mean duration of treatment episode 444 days compared with 288 days). In analyses considering this increased duration of OST, the overall adverse effect on mortality risk was still apparent (DRP with benzodiazepine concurrent prescription compared with patients with no concurrent exposure; adjusted IRR 4.04, 95% CI 2.35 to 6.95).

Sensitivity analyses were performed using survival analysis and Poisson regression excluding the first OST episode. Those results were consistent with those of the main analyses.

Interactions with opiate substitution treatment type and period

In the previous chapter, we found OST type to interact with a number of factors, including OST period, age and comorbidity. Consequently, it seemed plausible that OST type may also interact with these three co-prescribed medications. In addition, there were key questions concerning the timing of these medications relating to whether or not the exposure was concurrent with OST. A priori, one might have expected a greater effect concurrent with OST than during periods after OST has ceased. These issues were explored using an interaction with OST period.

The results from these analyses are summarised in *Table 18*. To take account of the possibility that OST period with four categories may be underpowered to detect concurrent specific effects, interactions were also fitted using a two-level factor reflecting on and off OST. Overall, there was no evidence of any interactions. The strongest evidence was for gabapentinoids with ACM. These data suggested that gabapentinoids had an adverse association with mortality for methadone only, with no effect for buprenorphine episodes. The interaction with period suggested an adverse effect only for the period of treatment after the first 4 weeks and the first 4 weeks after treatment cessation. However, given the number of statistical tests being employed, both of these results may be chance events.

TABLE 18 Interactions between co-prescribed medications and OST type or period

	All cause			Drug related			Non-drug related		
Medication	Type	Period4	Period2	Type	Period4	Period2	Type	Period4	Period2
B on/off	0.7437	0.4499	0.5014	0.2006	0.2781	0.5665	0.9805	0.7949	0.5811
B low/high	0.1051	0.3771	0.2885	0.6201	0.2054	0.2337	0.5236	0.9148	0.5807
B linear	0.3009	0.3954	0.2822	0.1505	0.4055	0.5145	0.7532	0.6707	0.4324
Z on/off	0.4284	0.3633	0.2646	0.1268	0.4070	0.7308	0.6749	0.6550	0.3995
Z low/high	0.5722	0.1932	0.0648	0.2565	0.8235	0.9106	0.8477	0.2834	0.0763
Z linear	0.6374	0.1633	0.0822	0.1765	0.6945	0.7636	0.7826	0.3953	0.1031
G on/off	0.0059	0.0022	0.0419		0.0979	0.0795	0.1412	0.1807	0.6647

B, benzodiazepines; G, gabapentinoids; Z, z-drugs.

Notes

OST type was coded as methadone or buprenorphine. OST period was coded as either four groups (on 1–4 weeks, on rest, off 1–4 weeks, off rest) or two groups (on, off).

Co-prescribed medications were modelled as on or off treatment with benzodiazepines and z-drugs were also analysed where on treatment was split as low or high (within or above recommended doses).

The interaction for gabapentinoids and OST type could not be fitted for DRP because zero deaths were observed for buprenorphine with gabapentinoid on treatment.

Analyses were adjusted for gender, age, year, comorbidity, region and, where applicable, OST type, OST period, benzodiazepine, z-drug and gabapentinoid exposure.

Co-prescription and the opiate substitution treatment type × period interaction

Given that the OST type propensity score included a contribution from co-prescription, it was expected that further adjustment for co-prescription would have little effect on this interaction. In addition, given the similarity in IPW analyses with standard Poisson regression for ACM, it might also be expected that these results would not be materially affected. These assumptions were verified in *Table 19*.

Summary

We found that co-prescription of benzodiazepines was associated with an increased risk of DRP. This was consistent with most studies,[26,28–30] although one found no association.[31] Although we also found weak associations with ACM, the evidence from other studies was more equivocal.[26,31,67] We found z-drugs and gabapentinoids to be associated with DRP, as found in one other study.[31] For ACM, our positive association was inconsistent with the only other study involving OST patients,[31] although there was some evidence of increased risk for these medications for opioid users.[32,33] Whether the association with gabapentinoids is a reflection of the medication itself or confounding by the illnesses it is trying to treat remains unclear.

Our results have implications for clinical practice for OST. With over one-quarter of OST patients receiving benzodiazepines, the increased mortality risk associated with their co-prescription suggests that this may include an avoidable number of risks if suitable alternative treatment can be found. For instance, if they have been prescribed for psychological stress, other means of support may be available. For z-drugs, similar drug-related mortality risks and higher ACM risks were observed in this study, suggesting that similar warnings concerning co-prescription are warranted for this class of medications. With the co-prescription of gabapentinoids being relatively rare in this study, and with few other studies examining these medications, the implications for policy are less clear for gabapentinoids.

TABLE 19 Poisson regression analyses of mortality adjusting for co-prescription

		All-cause mortality[a]		Drug-related mortality[a]	
Period	OST type	IRR (95% CI)	*p*-value	IRR (95% CI)	*p*-value
On 1–4 weeks		3.35 (2.44 to 4.60)	**< 0.0001**	3.24 (1.54 to 6.79)	**< 0.0001**
On rest		1 (reference)		1 (reference)	
Off 1–4 weeks		11.82 (9.58 to 14.57)		7.36 (4.22 to 12.83)	
Off rest		3.43 (2.82 to 4.17)		3.33 (2.12 to 5.25)	
On 1–4 weeks	Methadone	1 (reference)	**0.0007**	1 (reference)	**0.0799**
	Buprenorphine	0.04 (0.01 to 0.18)	< 0.0001	0.23 (0.03 to 1.83)	0.1643
On rest (reference)	Methadone	1 (reference)		1 (reference)	
	Buprenorphine	0.25 (0.16 to 0.39)	< 0.0001	0.37 (0.13 to 1.07)	0.0661
Off 1–4 weeks	Methadone	1 (reference)		1 (reference)	
	Buprenorphine	0.09 (0.06 to 0.15)	< 0.0001	1.49 (0.62 to 3.59)	0.3700
Off rest	Methadone	1 (reference)		1 (reference)	
	Buprenorphine	0.24 (0.17 to 0.33)	< 0.0001	0.43 (0.21 to 0.90)	0.0256

a Adjusted for gender, age, year, comorbidity, region, benzodiazepine, z-drug, gabapentinoids and, where applicable, treatment period and OST type.

Note

Main effect and interaction *p*-values (3 df) are shown in bold.

Chapter 7 Initiation and cessation of opiate substitution treatment

Initiation and cessation of OST are key periods in the treatment of opioid abuse when risks of overdose and withdrawal need to be minimised. Current clinical guidance recommends a low initial dose with steady increases to a maintenance level and gradual reduction in dose leading to a low final dose.[7,36] As adherence to these guidelines was poor, as seen in *Chapter 4*, in this chapter on WP 4, we explore whether or not these deviations had any adverse impact on mortality.

Aims and objectives

In this WP, we planned to investigate whether or not the risk of mortality is reduced with:

- supervised consumption of OST medication
- low initial doses with increasing doses over the first 28 days of treatment
- low final doses with decreasing doses over the last 28 days of treatment.

Our primary aims were to explore the associations of these factors with mortality during the first 28 days of treatment for initiation and the first 28 days following the end of treatment for cessation. Analyses would explore whether or not these associations differed by OST type.

In addition, we explored whether or not adherence to current guidelines for initiation and cessation varied over time.

Data set

As we were concerned with only the first or last 28 days of a treatment episode, we restricted episodes to those involving only methadone or buprenorphine during these times. The data used in these analyses related to 11,289 patients and 26,544 episodes (see *Figure 2*). However, owing to differing criteria for initiation or cessation (see *Initiation of opiate substitution treatment* and *Cessation of opiate substitution treatment*), and to some episodes being only partially included within the study period (and hence the initiation or cessation periods may be excluded), not all of these data were used in any one analysis.

Supervised consumption

From the supplied CPRD data, it was possible to identify supervised consumption only from the free text associated with each prescription. Searches revealed 4071 prescriptions, with 3831 using the phrase 'supervised administration' and 240 using 'supervised consumption'. These related to 184 patients and were all for methadone. Searches involving likely spelling mistakes or abbreviations discovered no additional prescriptions.

We requested CPRD to search its databases, including information not normally released. It identified 16,750 prescriptions for 591 patients for the whole database (not just our data set) covering the period 1987 to March 2015.

Overall, we concluded that the prevalence of supervised consumption was seriously under-reported and that using the available data would be underpowered to address research objectives as a result of both the low observed prevalence and the dilution of effects as a result of misclassification.

Initiation of opiate substitution treatment

We characterised the initiation of treatment using two measures: the starting dose and the change in dose during the first 28 days. Episodes were included in the analyses where only one medication was prescribed in the first 28 days, there was valid dose information for at least part of this time and some part of the first 28 days of treatment occurred between the study dates. This led to 10,817 patients providing data for 25,246 episodes.

Cessation of opiate substitution treatment

Similarly, ending dose and the change in dose over the last 28 days were used to describe cessation. Treatment could end by planned cessation, dropout or death. Episodes were included in the analyses where only one medication was prescribed during the last 28 days, there was valid dose information for at least part of this time, the duration exceeded 90 days and some part of the first 28 days following cessation occurred between the study dates. It should be noted that episodes were excluded where treatment had not ceased but data were unavailable owing to loss to follow-up. This led to 6491 patients providing data for 10,811 episodes.

Analyses

We investigated the impact of initiation and cessation characteristics on ACM and DRP.

Initiation and cessation characteristics were analysed both as linear covariates and as categorical factors to allow for non-linear effects. Methadone doses for the linear covariates were divided by five to achieve a dose more equivalent to buprenorphine. For starting/ending doses, a four-level factor was derived, with the lowest dose category defined as $\leq$ 20 mg ($\leq$ 4 mg) of methadone (buprenorphine) and increasing by 20 mg (4 mg) per category until the highest dose category of > 60 mg (> 12 mg). For change in dose, this was categorised as binary variables, with any increase in dose for initiation or any decrease in dose for cessation being expected to be more favourable in terms of mortality than no increase or decrease, respectively.

Although standard adjustment was made for gender, age, year, comorbidity and UK region, we also adjusted for OST type as an additional model. The inclusion of OST type allowed proportional effects (parallel effects on a log scale) to be investigated. Previous interactions with OST type have been observed in WP 2 and it seemed advisable also to consider the possibility that initiation and cessation characteristics might interact with OST type.

Adherence to the guidelines[7] was based on low starting or ending doses and optimal changes in dose during the first 28 days after either the start or the end of treatment.

Results

Initiation and cessation characteristics

The results from the linear growth models are shown in *Table 20*. Characteristics differed between methadone and buprenorphine. Both starting and ending doses for methadone episodes were evenly distributed across the four categories, with 21% to 27% of episodes being associated with the lowest dose. By contrast, for buprenorphine, ≈50% of episodes started or ended with the lowest dose category. Most episodes showed little evidence of any change in dose, with only about 30% of episodes showing increases during initiation or decreases during cessation. The exception appeared to be the change in dose for methadone episodes during the first 28 days. Here, 68% showed some increase in dose, but, as the mean suggests, the overall increases were small.

TABLE 20 Starting/ending doses and changes in dose during the first and last 28 days of episodes

Initiation (first 28 days)			Cessation (last 28 days)		
Daily dose	Methadone	Buprenorphine	Daily dose	Methadone	Buprenorphine
Lowest[a]	3564 (20.75)	3879 (47.27)	Lowest[a]	2258 (27.79)	1407 (51.31)
	6028 (35.10)	1701 (20.73)		1969 (24.24)	726 (26.48)
	4054 (23.61)	1488 (18.13)		1695 (20.86)	252 (9.19)
Highest	3527 (20.54)	1138 (13.87)	Highest	2202 (27.10)	357 (13.02)
Mean (SD)	42.56 (30.39)	6.08 (6.51)		43.12 (34.55)	5.57 (6.04)
n (episodes)	17,173	8206		8124	2742
Change in dose					
No increase	5494 (31.99)	5044 (61.47)	No decrease	5674 (69.84)	1934 (70.53)
Any increase	11,679 (68.01)	3162 (38.53)	Any decrease	2450 (30.16)	808 (29.47)
Mean (SD)	1.20 (23.29)	–0.28 (5.25)		2.87 (27.89)	0.25 (4.42)
n (episodes)	17,173	8206		8124	2742

a Daily dose categories were lowest ≤ 20 (≤ 4), > 20–40 (> 4–8), > 40–60 (> 8–12) and highest > 60 mg (> 12 mg) of methadone (buprenorphine).

Initiation and mortality

Only about 7% of the deaths available in WP 3 were valid for these analyses. This led to 48 ACM and eight DRP deaths (*Table 21*).

Higher starting doses were associated with an increased risk of ACM. Unadjusted results suggested a 7% increase in risk for every 5-mg increase in the starting dose of methadone (1-mg increase in buprenorphine) (HR 1.07, 95% CI 1.03 to 1.10). Adjustment for confounders and then OST type attenuated the results, but the association remained (HR 1.04, 95% CI 1.00 to 1.09). Categorising the starting dose may suggest that the biggest change in risk was exceeding low doses, although the CIs were too wide to obtain robust statistical evidence. There was some evidence that increasing the dose over the first 28 days also appeared to be beneficial, reducing mortality risks by 5% (HR 0.95, 95% CI 0.90 to 1.00).

An analysis of DRP produced similar results to that of ACM in terms of point estimates, with a 3% increase in risk being associated with the linear starting dose effect and a 7% reduction in risk for the linear change in dose effect. However, with only eight deaths, the CIs were wide and the statistical evidence weak.

There was no evidence that these effects varied between patients prescribed methadone and those prescribed buprenorphine (interaction $p > 0.39$).

Cessation and mortality

Only about 11% of the deaths available in WP 3 were valid for these analyses. This led to 75 ACM and 12 DRP deaths (*Table 22*).

For ACM, higher ending doses were associated with increased risk. Similar to initiation, adjustment attenuated linear effect sizes by about 50%. With full adjustment, the results were perhaps underpowered, but suggested a 3% increase in mortality risk associated with every 5-mg increase in ending dose of methadone (1-mg increase for buprenorphine) (HR 1.03, 95% CI 0.99 to 1.07). As for initiation, the biggest change in risk was to exceed the low dose. For DRP, adjustment amplified effect sizes, almost trebling the linear effect size. Here, there was a 17% increase in risk associated with every 5-mg methadone

TABLE 21 Cox regression results for initiation and the first 28 days of treatment

				Unadjusted			Adjusted[a]		Adjusted[a] + OST type	
Dose	Category	Deaths	PY	MR	HR (95% CI)	*p*-value	HR (95% CI)	*p*-value	HR (95% CI)	*p*-value
ACM										
Starting	Linear[b]				1.07 (1.03 to 1.10)	0.0001	1.05 (1.02 to 1.09)	0.0044	1.04 (1.00 to 1.09)	0.0413
Starting	Lowest[c]	13	434	3.00	1 (reference)	0.0795	1 (reference)	0.2168	1 (reference)	0.5574
		15	499	3.01	2.31 (0.99 to 5.34)		1.76 (0.65 to 4.76)		0.76 (0.25 to 2.28)	
		9	360	2.50	2.27 (0.87 to 5.92)		3.03 (0.99 to 9.21)		1.56 (0.48 to 5.08)	
	Highest	11	297	3.70	3.03 (1.27 to 7.26)		2.39 (0.86 to 6.69)		1.32 (0.45 to 3.90)	
Change	Linear[b]				0.94 (0.89 to 0.99)	0.0195	0.94 (0.89 to 0.99)	0.0238	0.95 (0.90 to 1.00)	0.0655
Change	No increase	14	650	2.15	0.54 (0.28 to 1.02)	0.0565	0.69 (0.33 to 1.45)	0.3249	1.04 (0.46 to 2.36)	0.9279
	Any increase	34	939	3.62	1 (reference)		1 (reference)		1 (reference)	
Drug-related mortality										
Starting	Linear[b]				1.02 (0.91 to 1.15)	0.6979	1.04 (0.88 to 1.23)	0.6227	1.03 (0.86 to 1.23)	0.7421
Starting	Lowest[c]	2	278	0.72	1 (reference)	0.8202	1 (reference)	0.4125	1 (reference)	0.3297
		3	296	1.01	1.33 (0.20 to 8.87)		0.21 (0.01 to 6.58)		0.02 (0.00 to 3.62)	
		2	215	0.93	2.72 (0.34 to 22.11)		3.52 (0.21 to 58.18)		2.16 (0.13 to 34.79)	
	Highest	1	148	0.67	1.73 (0.13 to 23.07)		0.97 (0.03 to 30.81)		0.32 (0.01 to 12.88)	
Change	Linear[b]				1.00 (0.81 to 1.25)	0.9902	0.97 (0.70 to 1.34)	0.8436	0.93 (0.68 to 1.27)	0.6436
Change	No increase	2	412	0.49	0.50 (0.08 to 3.01)	0.4479	0.98 (0.12 to 8.35)	0.9873	1.69 (0.18 to 15.59)	0.6447
	Any increase	6	525	1.14	1 (reference)		1 (reference)		1 (reference)	

HR, hazard ratio implicitly adjusted for age; MR, mortality rate (deaths/100 person years); PY person-years of follow-up.
a Adjusted for gender, calendar year, comorbidity score and region.
b Effect sizes are per 5-mg increase in methadone dose (1-mg increase in buprenorphine); linear effects relate to a log scale.
c Daily dose categories were lowest ≤ 20 (≤ 4), > 20–40 (> 4–8), > 40–60 (> 8–12) and highest > 60 mg (> 12 mg) of methadone (buprenorphine).

TABLE 22 Cox regression results for cessation and the first 28 days after the end of treatment

				Unadjusted			Adjusted[a]		Adjusted[a] + OST type	
Dose	Category	Deaths	PY	MR	HR (95% CI)	*p*-value	HR (95% CI)	*p*-value	HR (95% CI)	*p*-value
ACM										
Ending	Linear[b]				1.06 (1.03 to 1.09)	0.0001	1.04 (1.01 to 1.08)	0.0158	1.03 (0.99 to 1.07)	0.0926
Ending	Lowest[c]	8	273	2.93	1 (reference)	0.0005	1 (reference)	0.0262	1 (reference)	0.1041
		24	196	12.26	4.49 (1.94 to 10.42)		3.41 (1.41 to 8.26)		2.94 (1.21 to 7.13)	
		16	141	11.38	4.91 (1.98 to 12.21)		3.73 (1.44 to 9.65)		2.79 (1.06 to 7.35)	
	Highest	27	183	14.77	5.72 (2.46 to 13.30)		3.32 (1.35 to 8.17)		2.43 (0.97 to 6.10)	
Change	Linear[b]				1.00 (0.95 to 1.05)	0.9607	0.99 (0.93 to 1.05)	0.7257	0.99 (0.94 to 1.05)	0.7338
Change	No decrease	61	552	11.06	1.34 (0.71 to 2.53)	0.3674	1.35 (0.69 to 2.66)	0.3824	1.47 (0.73 to 2.95)[d]	0.2790
	Any decrease	14	240	5.83	1 (reference)		1 (reference)		1 (reference)	
Drug-related mortality										
Ending	Linear[b]				1.06 (0.97 to 1.16)	0.1833	1.08 (0.98 to 1.19)	0.1227	1.17 (1.02 to 1.33)	0.0209
Ending	Lowest[c]	3	166	1.81	1 (reference)	0.8374	1 (reference)	0.8032	1 (reference)	0.2426
		3	118	2.53	1.40 (0.27 to 7.33)		1.57 (0.20 to 12.14)		1.41 (0.16 to 12.28)	
		3	84	3.57	2.05 (0.38 to 11.04)		1.80 (0.32 to 10.21)		4.24 (0.63 to 28.66)	
	Highest	3	87	3.43	1.86 (0.36 to 9.68)		2.42 (0.39 to 14.94)		11.59 (0.93 to 144)	
Change	Linear[b]				1.00 (0.86 to 1.16)	0.9881	1.01 (0.85 to 1.21)	0.8935	1.03 (0.84 to 1.25)	0.8044
Change	No decrease	7	310	2.26	0.72 (0.22 to 2.40)	0.5932	0.69 (0.19 to 2.55)	0.5802	0.88 (0.22 to 3.52)	0.8555
	Any decrease	5	146	3.43	1 (reference)		1 (reference)		1 (reference)	

HR, hazard ratio implicitly adjusted for age; MR, mortality rate (deaths/100 person-years); PY, person-years of follow-up.
a Adjusted for gender, calendar year, comorbidity score and region.
b Effect sizes are per 5-mg increase in methadone dose (1-mg increase in buprenorphine); linear effects relate to a log scale.
c Daily dose categories were lowest ≤ 20 (≤ 4), > 20–40 (> 4–8), > 40–60 (> 8–12) and highest > 60 mg (> 12 mg) of methadone (buprenorphine).
d Interaction with OST type ($p = 0.022$), HR no decrease for methadone 2.00 (95% CI 0.90 to 4.42), for buprenorphine 0.26 (95% CI 0.05 to 1.24).

(1-mg buprenorphine) increase in ending dose (HR 1.17, 95% CI 1.02 to 1.33). Unlike ACM, the biggest change in risk may be associated with exceeding medium doses.

There was no evidence that changing dose over the last 28 days had any effect on mortality risks.

There was some evidence that the change in dose effect varied with OST type for ACM (interaction $p = 0.022$). Whereas no decrease in dose appeared to be associated with an increase risk by 100% for methadone ($p = 0.088$), there was a 75% reduction in risk for buprenorphine ($p = 0.091$) compared with any decrease.

Trends in adherence for initiation and cessation

Prior to the guidelines in 2007,[7] there was declining adherence or no change in adherence (*Table 23*). In particular, starting and ending doses and change in dose for methadone during cessation showed evidence of declining adherence. After the guidelines, this decline was generally halted for initiation starting doses and may be improving for most cessation characteristics.

Summary

Evidence that OST initiation and cessation followed current guidelines has historically been poor. Although there was evidence that adherence is improving, evidence of planned titration and discharge remains low. There was considerable variability in initiation and cessation characteristics. This may reflect errors in recorded or imputed daily doses, missing prescription data misclassifying one episode as two episodes or, for initiation, accelerated detoxification.

The trend towards lower starting and ending doses being associated with lower risk of mortality was found for ACM. For DRP, the same trends were observed but the evidence was weaker as result of the lack of power associated with few deaths. This is consistent with other studies reporting the lowest incidence of mortality among those starting on < 30mg/day methadone and those completing detoxification.[68,69]

We found weak evidence for a beneficial association on mortality risk for an increasing dose during the first 28 days of treatment. Although our data did not exhibit large rapid increases in dose, one study has reported an increased risk of mortality associated with too-rapid increases in methadone dose.[68] There was no evidence that changes in dose during cessation were associated with mortality. This may reflect that a period of 28 days was too short to capture optimal changes in dose.

Although it was interesting that effect modification for change in dose with OST type for cessation appeared to be present for ACM, the interaction was difficult to interpret and was probably a chance event among the multiple comparisons being tested.

TABLE 23 Trends in adherence to Department of Health and Social Care guidelines from 2001 to 2014

	Initiation [Total number of episodes (% adherence)]				Cessation [Total number of episodes (% adherence)]			
	Starting dose		Increase in dose		Ending dose		Decrease in dose	
Year	Methadone	Buprenorphine	Methadone	Buprenorphine	Methadone	Buprenorphine	Methadone	Buprenorphine
2001	1235 (25.51)	318 (60.38)	1235 (68.02)	318 (36.16)	463 (32.18)	69 (66.67)	463 (37.80)	69 (30.43)
2002	1291 (24.09)	497 (46.68)	1291 (67.70)	497 (35.01)	500 (29.40)	120 (56.67)	500 (33.60)	120 (30.00)
2003	1389 (21.74)	637 (44.90)	1389 (69.26)	637 (41.44)	509 (25.93)	180 (54.44)	509 (28.09)	180 (30.56)
2004	1271 (21.32)	718 (38.86)	1271 (67.19)	718 (37.19)	653 (27.72)	215 (55.35)	653 (28.02)	215 (29.77)
2005	1152 (22.14)	737 (41.79)	1152 (67.97)	737 (37.04)	564 (25.35)	242 (47.93)	564 (26.06)	242 (28.93)
2006	1209 (19.35)	718 (39.69)	1209 (68.73)	718 (39.00)	588 (25.17)	233 (43.78)	588 (27.21)	233 (33.91)
2007	1175 (20.68)	695 (44.03)	1175 (68.85)	695 (40.14)	533 (25.52)	243 (44.86)	533 (25.70)	243 (33.74)
2008	1200 (20.42)	648 (43.06)	1200 (68.58)	648 (36.88)	548 (24.27)	237 (43.88)	548 (25.91)	237 (29.96)
2009	974 (16.94)	625 (51.04)	974 (68.89)	625 (37.44)	542 (25.46)	202 (48.02)	542 (29.34)	202 (24.75)
2010	1024 (17.58)	552 (50.00)	1024 (71.09)	552 (41.85)	464 (27.37)	199 (42.21)	464 (30.60)	199 (26.63)
2011	797 (15.68)	496 (52.62)	797 (64.62)	496 (40.12)	519 (25.43)	182 (51.65)	519 (31.79)	182 (29.67)
2012	717 (18.27)	517 (48.16)	717 (66.11)	517 (40.81)	491 (27.90)	222 (54.95)	491 (30.14)	222 (35.59)
2013	624 (17.31)	432 (39.81)	624 (65.87)	432 (35.65)	393 (24.68)	199 (53.27)	393 (27.23)	199 (28.64)
2014	299 (23.41)	236 (44.49)	299 (66.56)	236 (37.71)	229 (25.33)	96 (52.08)	229 (26.20)	96 (30.21)
Trends								
2001–6	–0.061, 0.0002	–0.121, < 0.0001	0.003, 0.8416	0.015, 0.4874	–0.063, 0.0068	–0.156, 0.0002	–0.100, < 0.0001	0.025, 0.5648
2007–14	–0.021, 0.1576	0.002, 0.8808	–0.025, 0.0423	–0.004, 0.7914	0.007, 0.6688	0.066, 0.0041	0.019, 0.2671	0.000, 0.9946
Equality	0.0693	< 0.0001	0.1443	0.4692	0.0152	< 0.0001	< 0.0001	0.6185

Notes
Adherence was based on low doses for starting and ending doses. Trends are calculated by logistic regressions on the percentages adherent. The results are reported as the change in log-odds per calendar year with the *p*-value. The trends are calculated pre (2001–6) and post guidelines (2007–14). The equality of these trends is reported as an interaction *p*-value. Data for 1998–2000 were excluded because there were too few buprenorphine episodes.

Chapter 8 Development of self-controlled case series methods for opiate substitution treatment data

In this project we have attempted to use a number of methods to obtain more robust results. In this chapter, on WP 5, we describe the modification of two SCCS methods[48,50] and the results comparing these methods using simulations.

Aims and objectives

Self-controlled case series methods have been developed to study the adverse reactions to vaccinations.[48,50] In these scenarios, treatment episodes consist of a series of very short exposures (the injections) at regular intervals. This is in stark contrast to therapeutic data, where exposure times are variable and can last for months and where the sequence of episodes is not predetermined and will vary both in frequency and number.

In the context of OST data, there are two main problems. First, having a variable treatment period leads to an open-ended risk period following the first 4 weeks of treatment. This period would need to be estimated if death occurs during treatment. The equivalent open-ended period after treatment had ceased for more than 4 weeks was not originally considered to raise major issues. Second, there were two main types of treatment involving methadone or buprenorphine with their effects on mortality varying with the treatment period.

The aims of this WP were to extend existing methods to cater for these additional characteristics of OST data. We used simulations to verify that the modifications were robust and finally to apply the modified methods to the real data relating to WP 2 to investigate the OST type × period interaction.

The implications of these facets of the OST data are discussed in the next section as we describe some of features of the SCCS methods. Other characteristics of the OST data and their implications to SCCS analyses are described in the report under submission.

Implications of the existing self-controlled case series methods for opiate substitution treatment data

The two methods are referred to as the Farrington[48] and Kuhnert[50] methods, both of which are relevant to censored data as arise in the study of mortality. Both methods analyse only cases using fixed-effects Poisson regression clustering on patients. Using this technique has advantages in that the fixed effects can adjust for all non-time-varying factors, whether or not observed, associated with the patient. Both methods attempt to reconstruct the last episode, when death occurred, as if death had not occurred. In the context of vaccination data, this is straightforward, as typically there is a single risk period for each episode of fixed duration. Although the subsequent control period is technically open-ended, this is catered for differently by the two methods. For the Kuhnert method, there is usually a known earliest date for the next vaccination, whereas for the Farrington method there is usually a known date when follow-up was planned to cease. These dates are used to set the end of the control period.

Differences between the two methods reflect the exclusion of cases and the derivation of pseudo-individuals. For the Kuhnert method, patients who died after the earliest date for the next vaccination are excluded but all included patients appear only once. By contrast, for the Farrington method, all cases are included but copies of each patient's data are generated to reflect unobserved scenarios in which each observed treatment episode was the only episode to occur.

For the OST data, the open-ended treatment period was imputed using treatment duration data for patients who survived. Imputations were based on matched patients receiving the same medication at a similar time and of a similar age to those patients who died. For the open-ended period after treatment ceased, a date 1 year after the last treatment ended was used for the Farrington method. For the Kuhnert method, although 28 days was the observed minimum interval between treatment episodes, this interval was too short to allow estimation of the open-ended period. Hence, a range of intervals from 35 to 56 days was tried.

The presence of two medications had consequences for estimating the type × period interaction. Because only one episode and hence one medication was used for all patients in the Kuhnert method and all pseudo-individuals in the Farrington method, 1 df was aliased between the interaction and the clustered fixed effect. To overcome this, the open-ended off-treatment period was assumed to be equal for methadone and buprenorphine.

Data set used in simulations

Data relating to 11,033 patients as used in WP 2 were also used in this WP, but instead of using the observed deaths, simulated deaths were generated using the observed risks for covariates obtained from WP 2 using Poisson regression. In all, 1000 simulated data sets were generated, producing results for both methods under different scenarios.

Key findings from the submitted paper

Simulations suggested that the Farrington method, assuming a projected end to follow-up of 150 days after the last treatment ended, produced estimated effects closest to the true values. For the Kuhnert method, the shortest interval performed best, although the differences between 35 and 56 days were small. This characteristic was important, as there may be insufficient numbers of death for shorter intervals to allow the interactions to be modelled.

Using these modified methods with the observed data allowed comparisons with an alternative robust method, IPW, as reported in WP 2.[61] For ACM, these methods also showed evidence of a OST type × period interaction, although stronger evidence came from the Farrington method, probably because of the greater number of deaths that were valid for this method. There was perhaps some deviation from results reported in WP 2 in that differences between methadone and buprenorphine were smaller and statistically equivalent for the period following the first 4 weeks of treatment for the Farrington method (interaction IRR 1.04, 95% CI 0.55 to 1.94) and for the Kuhnert method (interaction IRR 2.34, 95% CI 0.56 to 9.84). At other times, as reported in WP 2, buprenorphine was protective compared with methadone. For DRP, no evidence of an interaction was found with either method, in contrast to results from IPW analyses. However, SEs were large in these analyses, making the detection of any potential interaction effects difficult.

Summary

Simulations have suggested that modifications to the SCCS methods have produced robust results. As a consequence, these methods can be applied not only to vaccination data but also to therapeutic prescription-based data. This may be particularly helpful for databases that contain limited additional information on patients' histories, severity of symptoms and treatment quality. However, robust results were achieved only with a relatively short intertreatment gap for the Farrington method and a very short gap for the Kuhnert method, although, for the Kuhnert method, this was to be expected as this interval should reflect the minimum gap between treatment episodes. The use of such constraints inevitably reduced the number of analysed deaths. Applying the revised methods to the observed data on mortality

and episodes of methadone and buprenorphine treatment reduced the number of deaths in the constrained sample by about 10% for the Farrington method and about 30% for the Kuhnert method compared with the original Poisson regressions reported in *Chapter 5*. The results suggested an OST type × period interaction for ACM but were too underpowered to evaluate DRP.

Chapter 9 Conclusions

This chapter considers the implications for clinical practice arising from the results of this study, a review of the potential limitations of this study and recommendations for future work.

Patient and public involvement

Our patient and public involvement (PPI) work demonstrates why we need to be very cautious in drawing conclusions on which form of OST is safer and more likely to reduce mortality risk in the population (see *Appendix 3* for more details). Drug workers and people who use opioids highlighted that there may be multiple reasons why people who choose or are prescribed buprenorphine are different from people who choose or are prescribed methadone, in terms of stability, mood and use of heroin and other drugs during treatment. For this reason, our PPI group were not surprised that fewer people died in the first 4 weeks of buprenorphine treatment than methadone treatment – even after adjustment for multiple confounders (differences in patient and practice characteristics between patients on methadone and those on buprenorphine). There was some, but not widespread, support for a trial that seeks to induct all patients onto buprenorphine where patients did not express a strong preference for methadone. However, others raised concerns over the probable need for additional psychological support and the potentially unintended consequences of such a trial (in terms of patients withdrawing from treatment or moving services). The PPI group confirmed that there is no clear and quick fix to reduce drug-related deaths in the population through changing the way in which OST is delivered. More development is needed to establish an acceptable intervention and trial of OST delivery (see *Chapter 9*, *Future research*).

Drug-related poisoning and all-cause mortality rates

The average annual ACM and DRP in our study, at 1.9% and 0.8%, respectively, were slightly higher than in some earlier studies of mortality in cohorts obtained from community drug treatment agencies (0.34 per 100 person-years based on the NDTMS[30,44]), although our findings were consistent with recent systematic review evidence.[64] It is likely that the NDTMS population is a mix of opioid users who may not all be receiving OST, in contrast to the CPRD population, which comprises people with opioid disorders in OST. There may also be differences in morbidity between CPRD and NDTMS populations, but we lack consistent data between the two systems to allow us to compare morbidity (see *Future research*).

Clinical implications and recommendations

Our data suggest that there was an increased risk of mortality during the first 4 weeks of treatment, with lower risks being associated with buprenorphine treatment. Although this may suggest advantages in prescribing buprenorphine during induction and switching to methadone later if necessary, our investigations into such strategies showed only a low probability of reducing DRP.

The increased risk of ACM mortality following cessation of treatment may indicate poor retention in treatment or the need for greater patient support when the impact of reduced opioid tolerance is most acute. The lower risk for buprenorphine during this period may suggest benefits in switching to buprenorphine during the final stages of treatment.

We identified particular groups of patients in our data, namely those who were older and had more comorbidity, who appeared to particularly benefit from buprenorphine treatment. This was a novel result and not specified a priori. Further work is needed to confirm these interactions.

As in other studies, our study also suggested shorter treatment duration for buprenorphine than methadone treatment, but the intervals between treatments also differed, with buprenorphine having a shorter off-treatment duration. Overall, current estimates indicate that buprenorphine patients have a lower percentage time on treatment. There is a clear public health need to retain people on OST longer to reduce the number of deaths in the population.

Our findings do not advocate prescribing benzodiazepines or z-drugs to OST patients. Gabapentinoids may also be detrimental, but further replication is needed. Although trends differed by medication, with benzodiazepine decreasing and gabapentinoids increasing in prevalence during the study period, overall, for each of these three medications, data since 2002 have suggested that the prevalence of affected patients remained constant. Our data would suggest that further decreases in co-prescribing would be beneficial.

Our analyses were completed before new clinical guidance on drug treatment was issued.[43] This guidance suggested caution in prescribing OST to patients if there is associated alcohol or benzodiazepine dependence, or use of other depressant drugs such as pregabalin or gabapentin or some major tranquillisers. Our findings have shown similar problems in prescribing benzodiazepines, z-drugs or gabapentinoids to patients with an ongoing opioid disorder irrespective of whether they are on or off OST.

Unfortunately, other critical aspects of OST delivery in CPRD data could not be measured, such as supervised consumption, availability and intensity of adjunct psychosocial support, and frequency of care-plan assessments during OST. Further research and alternative methodological approaches are required to measure the intensity and quality of OST on retention and mortality outcomes. It was found, however, that very few OST episodes seem to correspond to maintenance therapy, as such a large proportion of OST episodes lasted < 3 months. Furthermore, only a minority of OST episodes lasting < 3 months had any evidence of tapering of dose indicative of planned discharge and detoxification. The guidance suggests that 'duration of maintenance should reflect the patient's own preferences and their clinical circumstances (which may include the opportunities available to them to support their recovery and management of risk)' (contains public sector information licensed under the Open Government Licence v3.0).[43] It has been shown that, in the majority of episodes, OST is ceased prematurely and that there is a need to provide additional interventions to retain people on OST to achieve population benefit of reducing drug-related deaths. Short OST episodes are not unique to primary care, as we show when comparing average treatment duration between CPRD and a major non-governmental organisation.

Limitations of the study design, data sources and analytic methods

The key limitation of this project was the potential for residual confounding through either imperfectly measured observed confounders or omitted/unobserved confounders. Several analytic approaches have been presented to consider the extent of confounding, to aid interpretation of the analyses and to reduce the bias from such effects. These analyses, such as IPW, tended to strengthen confidence in the results.

There were likely to have been missing prescriptions in the CPRD data. For instance, some patients may have been treated in specialist drug treatment clinics as well as in primary care. Treatment during periods in prison are also unlikely to be recorded in primary care. This would lead to not only misclassification of periods on and off treatment but also possibly misclassification between the first 4 weeks and the remainder of time on treatment if the missing data had erroneously led to one episode being considered as two. To explore this further, sensitivity analyses were performed using different criteria for the derivation of episodes, but the impact on the OST type × period interaction was small. These misclassification of treatment periods would have also biased mean on- and off-treatment durations. However, it was expected that median durations would have been less susceptible to any bias.

Periods in prison may also introduce bias and confer additional risks; for example, the period in prison will be one of lower mortality risk but the period immediately following prison release is of high risk.[70] However, prison history was incorporated into the propensity scores as a method of reducing this bias.

The small number of DRP deaths among a high-risk group such as OST patients may indicate that these deaths were under-reported. Although this allowed some conclusions to be drawn relating to the OST type × period interaction and other interactions with age and comorbidity, other analyses on initiation and cessation were severely hampered.

Critically, it was not possible to characterise the intensity and quality of OST, and clinical data on addiction severity or drug use patterns over the 16 years of this study. However, these data are also absent from all other large-scale drug treatment cohorts. For example, treatment cohorts in New South Wales have fewer confounders than CPRD and adjusted only for age, gender and treatment history; and NDTMS lacks data on morbidity and detailed information on type of OST.[30,53] There is a clear tension between well-characterised cohorts or trials of OST and power to detect changes in mortality risk, and it seems unlikely in the immediate future that refined clinical information can be obtained on large numbers of patients. An alternative approach, undertaken in the VEdeTTE study,[17] is to conduct nested case–control studies within the cohort, and to collect more detailed clinical information on a smaller number of cases (DRP) and controls (three or four people with an opioid disorder who at the time of the case were known to be alive) (unpublished document: Professor Fabrizio Faggiano, University of Eastern Piedmont, and Dr Marina Davoli, Lazio Regional Health Service Rome 2018).

Since 2007 there have been changes to drug treatment and policy.[7,36,71] These include a greater emphasis on recovery and re-engagement with the community through employment, take-home naloxone to counteract overdose and a greater diversity of treatment agencies. These factors potentially may confound our results, particularly the longitudinal trends.

Future research

The results from this project suggest four main areas of future research.

First, replication and strengthening power: the analyses on DRP were limited because only just above half of the patient episodes were linked to Office for National Statistics data on cause of death. Several of the analyses involving SCCS methods and for initiation and cessation were underpowered and may provide clearer evidence if conducted on a larger data set. In addition, novel interactions between age and OST modality and between comorbidity and OST modality were identified that need to be tested in other data sets and studies.

Second, cross-cohort comparison: these results relate to UK primary care. There are benefits (in terms of both replication and identifying potential differences in OST delivery that may increase or decrease mortality risk) of comparing the CPRD findings with those for cohorts from community drug agencies in the UK and internationally. This will test whether there are differences between mortality risk in patients managed in primary care and those managed by community drug agencies, as well as raise hypotheses on how OST might be better delivered in the UK if differences are found across international cohorts.

Third, intensity of treatment: additional studies are needed both to determine the extent to which OST is delivered as recommended in current guidelines and to assess whether or not intensity of OST, including adjunct interventions, protects against DRP during and immediately after treatment cessation compared with low-intensity/low-threshold OST.

Fourth, interventions: retention in OST is critical to reducing the number of DRP in the population, and more work with patient groups and clinicians is required on how to deploy buprenorphine and methadone and other strategies both to reduce mortality risk at the beginning of OST and to retain patients on OST for prolonged periods to minimise mortality risk long enough to generate public health benefit.

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Contributions of authors

Colin D Steer (Senior Research Fellow, Medical Statistics) contributed to the analysis plan, the development of SCCS methods, the drafting of the report, the interpretation of the results and the critical revision of the report; he analysed the CPRD data and performed the SCCS simulations.

John Macleod (Professor of Clinical Epidemiology and Primary Care) contributed to the study design, the drafting of the report, PPI, the interpretation of the results and the critical revision of the report.

Kate Tilling (Professor of Medical Statistics) contributed to the analysis plan, the interpretation of the results and the critical revision of the report.

Aaron G Lim (Senior Research Associate, Infectious Disease Mathematical Modelling) performed the simulations of different treatment regimens on mortality rates, and contributed to the interpretation of the results and the critical revision of the report.

John Marsden (Professor of Addiction Psychology) contributed to the interpretation of the results and the critical revision of the report.

Tim Millar (Professor of Substance Use and Addictions) analysed treatment duration from a special drug agency database for comparison with CPRD, and contributed to the interpretation of the results and the critical revision of the report.

John Strang (Head of Addictions Department, Professor of the Psychiatry of Addictions) contributed to the interpretation of the results and the critical revision of the report.

Maggie Telfer (Chief Executive Officer of Bristol Drugs Project) contributed to PPI.

Heather Whitaker (Senior Lecturer, Statistics and SCCS methods) contributed to the development of SCCS methods for the CPRD data, the interpretation of the results and the critical revision of the report.

Peter Vickerman (Professor of Infectious Disease Modelling) contributed to the simulations of different treatment regimens on mortality rates, the interpretation of the results and the critical revision of the report.

Matthew Hickman (Head of Population Health Sciences, Professor in Public Health and Epidemiology) contributed to study design, the drafting of the report, the analysis plan, PPI, the interpretation of the results and the critical revision of the report.

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Data-sharing statement

This study utilised CPRD data that cannot be disseminated further as a result of conditions attached to their initial release to the authors. These data can be requested directly from CPRD (www.cprd.com). All queries should be submitted to the corresponding author.

Patient data

This work uses data provided by patients and collected by the NHS as part of their care and support. Using patient data is vital to improve health and care for everyone. There is huge potential to make better use of information from people's patient records, to understand more about disease, develop new treatments, monitor safety, and plan NHS services. Patient data should be kept safe and secure, to protect everyone's privacy, and it's important that there are safeguards to make sure that it is stored and used responsibly. Everyone should be able to find out about how patient data are used. #datasaveslives You can find out more about the background to this citation here: https://understandingpatientdata.org.uk/data-citation.

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Appendix 1 Definition of drug-related deaths

Description	ICD-9 codes	ICD-10 codes
Mental and behavioural disorders		
Attributable to drug use (excluding alcohol and tobacco)[a]	292, 304, 305.2–305.9	F11–F16, F18–F19
Unspecified cause/disorder		F99
Accidental self-harm		
Poisoning by drugs, medicaments and biological substances[a]	E850–E858	X40–X44
Poisoning, other or unspecified exposure	E866.8, E866.9	X49
Other or unspecified means	E928.8, E928.9	X58, X59.9
Intentional self-harm		
Poisoning by drugs, medicaments and biological substances[a]	E950.0–E950.5	X60–X64
Poisoning, other or unspecified exposure	E950.9	X69
Other or unspecified means	E958.8, E958.9	X83, X84
Assault by		
Poisoning by drugs, medicaments and biological substances[a]	E962.0	X85
Poisoning, other or unspecified exposure	E962.9	X90
Other or unspecified means	E968.8, E968.9	Y08, Y09
Self-harm, undetermined intent		
Poisoning by drugs, medicaments and biological substances[a]	E980.0–E980.5	Y10–Y14
Poisoning, other or unspecified exposure	E980.9	Y19
Other or unspecified means	E988.8, E988.9	Y33, Y34
External cause		
Poisoning by drugs, medicaments and biological substances	960–979	T36-T50
Poisoning, other or unspecified exposure	989.89, 989.9	T65.8, T65.9
Other or unspecified cause	995.89	T78.8, T78.9
Ill-defined, unspecified or unknown cause	798.1–798.9, 799.89, 799.9	R68.8, R69, R96–R99

a Office for National Statistics[54] (p. 33).

Appendix 2 Definition of psychosocial adversity using Clinical Practice Research Datalink medcodes

Self-harm

medcode	Description
10057	Deliberate self-harm
10464	Self-harm
17046	[X]Intentional self-harm
22107	[V]Personal history of self-harm
32267	Self-mutilation
35123	Self-mutilation of hands
45796	[X]Sequel intentn self-harm assault+event of undeterm intent
57479	Self-mutilation of genitalia
64200	Self-mutilation of ears
69263	[X]Sequelae of intentional self-harm

Overdose

medcode	Description
171	Overdose of drug
1493	Cause of overdose – accidental
6595	Cause of overdose – deliberate
11708	Overdose of biological substance
13568	H/O: repeated overdose
18379	[X]Overdose – paracetamol
28710	[X]Overdose – heroin
29861	[X]Overdose – aspirin
34703	[X]Overdose – amitriptyline
44886	[X]Overdose – ibuprofen
45748	[X]Overdose – diazepam
46280	[X]Overdose – antidepressant
48324	[X]Overdose – benzodiazepine
49552	[X]Overdose – barbiturate
51381	[X]Overdose – temazepam
52931	[X]Overdose – nitrazepam
55395	[X]Overdose – sleeping tabs
60559	[X]Overdose – SSRI
94725	[X]Overdose – amobarbital
99775	Intentional overdose of prescription only medication

Alcohol problems

medcode	Description
1399	Alcohol problem drinking
2081	Alcoholism
2082	Alcohol withdrawal syndrome
2083	Alcohol detoxification
2084	Alcohol dependence syndrome
2925	Alcoholic polyneuropathy
3216	Acute alcoholic hepatitis
4500	Korsakov's alcoholic psychosis
4506	Alcoholic gastritis
4743	Alcoholic cirrhosis of liver
4915	Alcoholic cardiomyopathy
5611	[X]Mental and behavioural disorders due to use of alcohol
5740	Acute alcoholic intoxication in alcoholism
5758	[X]Chronic alcoholism
6169	Alcohol dependence syndrome NOS
6467	[X]Alcoholic hallucinosis
7123	[V]Personal history of alcoholism
7602	Chronic alcoholic hepatitis
7885	Alcoholic liver damage unspecified
7943	Alcoholic hepatitis
8030	[V]Alcohol abuse counselling and surveillance
8363	Oesophageal varices in alcoholic cirrhosis of the liver
8388	[V]Alcohol rehabilitation
8430	H/O: alcoholism
9169	[D]Alcohol blood level excessive
9489	Under care of community alcohol team
9508	[X]Acute alcoholic drunkenness
9849	Referral to community alcohol team
10463	[X]Intent self poison/exposure to alcohol
10691	Alcoholic fatty liver
11106	Korsakov's alcoholic psychosis with peripheral neuritis
11670	[X]Korsakov's psychosis, alcohol induced
11740	Alcohol misuse – enhanced services administration
12353	[X]Mental & behav dis due to use alcohol: psychotic disorder
12554	Referral to community drug and alcohol team
12976	Suspect alcohol abuse – denied
12982	Alcohol intake above recommended sensible limits
16225	Alcohol withdrawal delirium
16237	Alcoholic psychoses
17259	[X]Delirium tremens, alcohol induced
17330	Alcoholic hepatic failure

medcode	Description
17607	[X]Alcoholic psychosis NOS
18156	Alcoholics anonymous
18252	Accidental poisoning by alcohol, NEC
19217	Alcohol causing toxic effect
20514	[X]Mental and behav dis due to use alcohol: withdrawal state
20762	Alcohol amnestic syndrome
21412	Adverse reaction to alcohol deterrents
21624	Episodic acute alcoholic intoxication in alcoholism
21650	Admitted to alcohol detoxification centre
21713	Alcoholic fibrosis and sclerosis of liver
21879	[X]Mental and behav dis due to use of alcohol: harmful use
23978	[X]Evid of alcohol involv determind by level of intoxication
24064	Continuous chronic alcoholism
24485	Chronic alcoholism in remission
24984	Alcohol-induced chronic pancreatitis
25110	Alcohol withdrawal hallucinosis
26106	Episodic chronic alcoholism
26323	[X]Alcoholic dementia NOS
27342	Alcoholic dementia NOS
28780	[X]Alcohol addiction
29691	Aversion therapy – alcoholism
30036	[X]Poisoning/exposure, ? intent, to alcohol
30162	[X]Alcoholic paranoia
30404	Alcoholic paranoia
30460	Alcoholism counselling
30604	Alcohol-induced epilepsy
31443	Chronic alcoholism
31605	[X]Accident poisoning/exposure to alcohol
31742	Alcoholic myopathy
32927	[X]Alcohol withdrawal-induced seizure
33635	Chronic alcoholism NOS
33839	Cerebellar ataxia due to alcoholism
36296	Acute alcoholic intoxication in alcoholism NOS
36499	Alcohol causing toxic effect NOS
36687	Alcohol deterrent poisoning
36748	Alcoholic encephalopathy
37691	[X]Chronic alcoholic brain syndrome
37946	Chronic alcoholic brain syndrome
38061	Alcohol induced hallucinations
39327	[X]Mental and behav dis due to use alcohol: dependence syndr
39799	[X]Mental and behav dis due to use alcohol: amnesic syndrome
40530	Acute alcoholic intoxication, unspecified, in alcoholism
40541	Accidental poisoning by alcoholic beverages

APPENDIX 2

medcode	Description
41638	[X]Int self poison/exposure to alcohol at home
41920	Alcohol amnestic syndrome NOS
41983	Alcohol detoxification
43193	Unspecified chronic alcoholism
44299	[X]Mental & behav dis due to use alcohol: acute intoxication
45169	[X]Men & behav dis due to use alcohol: oth men & behav dis
46677	Alcohol withdrawal regime
47555	Cerebral degeneration due to alcoholism
48241	[X] Adverse reaction to alcohol deterrents
48514	Denatured alcohol causing toxic effect
55415	Accidental poisoning by alcohol NOS
56410	Delivery of rehabilitation for alcohol addiction
56947	Continuous acute alcoholic intoxication in alcoholism
57714	Alcohol dependence with acute alcoholic intoxication
57939	Pathological alcohol intoxication
59414	[X]Intent self poison alcohol unspecif place
59574	Acute alcoholic intoxication in remission, in alcoholism
60752	Accidental poisoning by secondary propyl alcohol
61187	[X]Accid poison/expos to alcohol unspecif place
61190	[X]Pois/expos ?intent to alcohol unspecif place
63306	[X]Accident poison/exposure to alcohol at home
63529	Alcohol misuse – enhanced service completed
63876	[X]Accid poison/expos alcohol in street/highway
64389	[X]Ment & behav dis due use alcohol: unsp ment & behav dis
65754	Alcohol-induced pseudo-Cushing's syndrome
65932	[X]Alcoholic jealousy
67651	Alcoholic psychosis NOS
68159	[X]Poison/exposure ?intent, to alcohol at home
69407	[X]Pois/exp ?intent alcohol school/pub admin area
73876	[X]Alcohol deterrents caus adverse effects in therapeut use
92908	[X]Accid poison/expos alcohol trade/service area
94553	Referral to specialist alcohol treatment service
94670	Alcohol misuse
95181	Alcohol reduction programme
96053	Brief intervention for excessive alcohol consumptn completed
96054	Extended intervention for excessive alcohol consumptn complt
96219	[X]Pois/expos ?intent alcohol in street/highway
96993	Referral to alcohol brief intervention service
103069	[X]Acc poison/expos alcohol school/pub admin area
104611	Alcohol-induced acute pancreatitis
104702	[X]Accid pois/expos alcohol in sport/athletic area

NEC, not elsewhere classified; NOC, not otherwise specified.

Prison

medcode	Description
1123	In prison
10269	Released from prison
21521	Prison record
26013	Prison sentence
28655	[V]Imprisonment
29760	[V]Problems related to release from prison
37738	Imprisonment record
52682	Prison medical examination
53439	[V]Prison medical
54399	Place of occurrence of accident or poisoning, jail
59330	Place of occurrence of accident or poisoning, prison
105175	Medically fit for activity outside prison

Homeless

medcode	Description
2562	Homeless
25452	Homeless single person
67112	Homeless – enhanced services administration
96605	Homeless – enhanced service complete
97757	Sofa surfer – person of no fixed abod
104962	Length of time homeless
107393	Under care of homeless advocacy service

Appendix 3 Report on public and patient involvement

Evaluating the impact of opiate substitution treatment on drug related deaths in the population: a natural experiment using primary care, other drug treatment databases & model projections (NIHR OST DRD Project)

Patient Participation and Involvement – Bristol and Blackpool June – August 2016

Method

PPI was conducted by 2 members of staff at Bristol Drugs Project during August 2015. Staff and service users were interviewed in small groups each by two facilitators. Service users were reimbursed £15 cash for their time. Each focus group lasted approximately 1 hour.

Bristol – Members of staff from BDPs Shared Care service were interviewed in two groups and members of DHI (Developing Health and Independence) Peer Support group were interviewed in 1 group.

Blackpool – 3 groups of current service users and staff from Horizon Drug and Alcohol Service were interviewed at the premises; 49-55 Cookson Street, Blackpool FY1 3DR. Groups were arranged by staff from ADS Addiction Dependency Solutions

Rationale for approach used:

Outcomes data taken from a Lay Summary provided by M Hickman was presented to the staff groups in Bristol (Appendix I). The complexity of the data lead us to present data to subsequent groups in a further simplified PowerPoint, in agreement with MH (Appendix II).

Three reports are presented:

1. 2 staff groups from Bristol Drugs Project, Bristol (combined data),
2. 1 group of Peers, DHI, Bristol
3. 3 groups of service users and staff, from Blackpool (combined data).

Content

Rachel Ayres, Louisa Chowen - Bristol Drugs Project – Engagement Team

PPI for NIHR OST project

27 June 2016

Shared Care practitioners x 2 groups combined answers (18 staff)

Question 1

What other important differences could there be between people starting OST with Methadone or Buprenorphine?

- More 'On top' use possible with Methadone
- Cultural differences around attitudes to taking Methadone / Buprenorphine e.g. social group uses Methadone therefore client also wants to use Methadone
- Buprenorphine has an Anti-depressant element which could help stabilise clients mood
- Clients who choose Buprenorphine are less ambivalent about making changes to their illicit using
- Clients who choose Buprenorphine are more stable with less historic trauma
- The data should look at supervised vs unsupervised consumption
- Would expect B to be provided to more unstable/chaotic clients
- Chaotic meaning mental health problems
- Mental health must be looked at
- Sedating effect of methadone is seen to be more helpful for complex clients
- Clients saying "I'm not ready to stop – unlikely to be prescribed B Need to know about continued 'on top' use to understand this data Missing data:
- continued I/V use
- co-existing Mental health problems
- Co-morbidity index mainly physical - - no mention of mental health
- Looking at how much people are using at Assessment is important
- Has length of using history been looked at (not just age)
- If clients are seeking oblivion – they are more likely to seek Methadone
- More comfort in Methadone
- Victims of Sexual abuse or trauma more likely to want methadone
- People with family history of drug use will want methadone
- Looked at geographical but should look at socio-economic grouping
- Can we look at who is initiating the PX GP or drugs worker – feeling that GP more likely to initiate onto methadone
- Should look at how much support client is getting in first 4 weeks
- Should look at co-use of Crack
- Should look at illicit use of benzos – more erratic

Question 2

What do you think of the findings? (with particular reference to the 1st four weeks on treatment and 1st four weeks after treatment has ended)

- 1st four weeks safer on Buprenorphine but Methadone safer 1st four weeks after treatment
- What psycho social treatment had patients done and was this taken into account?
- Had past trauma been taken into account?
- Practitioners tended to express that clients who had chosen to be on Buprenorphine were likely to be more stable and more ready to make changes to their drug use
- Totally not surprised at results
- Clients on B tend to be more stable
- Circular argument – more stable clients – less like complications
- B is safer anyway – did anyone in the study die from B overdose?
- Thought the data might have shown even bigger differences
- 1st 4 weeks off (*noticing slight increased risk from Overdose with B)* clients on B may experience increased expectations of success from professionals and self and find it more difficult to return to treatment. May bee relapse and failure and fear of judgements – more likely to relapse and not seek help?
- Easy to disappear and keep coping if ending/ or falling off a Buprenorphine script.
- Is being on a methadone script still safer than not being on OST if you are an injecting opiate user? (despite this data)

Question 3

What needs to be done to test the hypothesis that Buprenorphine is safer than Methadone?

- Does this data include multiple presentations of same patients? Conduct a long term study of patients of 1-2 years Is being on anything safer than being on nothing?
- Must look at the length of time in (and out) of treatment (not just age) Look at number of episodes

Question 4

Your views on the proposed study

- Unethical as it reduces choice for the client
- Possibility of clients opting out of OST treatment completely
- Would need to measure OD rate of clients not in OST treatment at all
- Despite the evidence of this data, the practitioner can make a better, more experienced decision about OST which enhances better/safer outcome

Cluster trial

- If you do this – must compare similar socio economic groups, Bristol and Liverpool (i.e. not Bristol and Herefordshire)
- Is a cluster trial ethical now we know this data?

- Worried about unintended consequences of a trial – forcing people onto buprenorphine knowing they can't mange this regime
- Cluster trial – people would walk away and not get treatment
- No Treatment as Usual for those opting not to have buprenorphine for first 4 weeks
- I would feel uncomfortable being a shared care worker in a Buprenorphine only cluster (1 experienced worker)
- I would be happy to initiate everyone onto buprenorphine (1 experienced S/C worker)
- I can't think of anyone I have thought are Inappropriate for buprenorphine who has asked for it (experienced S/C worker)

RCT

- People who opt for the trial may have an interest in doing better (*because they don't mind being in the trial*)
- People would withdraw from the trial after randomisation if they didn't get the treatment they wanted (*based on knowledge that patients consenting to trials can withdraw at any point)*
- RCT would self select people who are already OK with buprenorphine

Question 5

Other views / comments

- Clients who choose not to be part of the cluster trial – how will their outcome be measured
- Clients who accept trial more likely to be more engaged and therefore likely to have better outcomes
- Is cluster trial ethical now we have the data
- Is there data on OD deaths for people who never access OST

PPI for NIHR OST project

27th June 2016

DHI Peer Support Workers (9)

Question 1 What do you think of the findings? (with particular reference to the 1st four weeks on treatment and 1st four weeks after treatment has ended)

- It makes sense. The mind set on Buprenorphine is that you want to stop
- If you aren't in the fellowship etc., even if you are on Buprenorphine you might use again
- Buprenorphine needs more support because it (using) gets less euphoric – when you have life issues, it's scary
- Methadone gives warm comfy feeling so prefer it
- If you use Buprenorphine in prison (sniff it) get a buzz – could want that in the community and be disappointed
- Some people do prefer Buprenorphine – If I sniffed or injected it I would get a buzz
- People who choose Buprenorphine initially are wanting to stop – but they need more support to cope on it
- It's clearly obvious that Buprenorphine is safer because of the mind set of the people on it
- Motivation to be on Buprenorphine in the first 4 weeks is high but can go off as time goes by
- Some people get what they need from Buprenorphine (clarity)
- 1st 4 weeks after treatment on Buprenorphine is really hard – psychologically – if you have been on Buprenorphine for a long time
- If you've been on Methadone a long time, you want the effect of heroin when you come off

  Did you look at what treatment (psycho social support) people were in around their OST?
- 1st 4 weeks off treatment are crucial – we need (support) or we will stray
- If you are on Methadone, you will have been on it for a very long time

Question 2

What other important differences could there be between people starting OST with Methadone or Buprenorphine?

- Different services tell you that Buprenorphine blocks at different doses – I would just smoke (heroin) until I overcame the blocking

- When homeless I didn't care which OST I had, I would take anything
- I didn't want Buprenorphine because it would mess with my using
- I chose Methadone when I didn't want to stop using
- Only chose Buprenorphine when I wanted to stop using
- When I wanted to stop I stopped
- If you are on a whack of methadone, it didn't do anything if you used on top I was on Buprenorphine because I wanted to stop

Question 3

What needs to be done to test the hypothesis that Buprenorphine is safer than Methadone?

- Why not put people on Buprenorphine in 1st 4 weeks?
- How long were people on Buprenorphine / Methadone?
- My money is on people on Methadone will have been in (OST) treatment for much longer
- Must find out length of (OST) treatment
- What about the people on long term Methadone being put on Buprenorphine?
- Could put everyone on Buprenorphine but they would need masses of support

Question 4 Your views on the proposed study

- If clustered in Bristol – people will move surgery
- RCT people who want Methadone will decline the trial
- If a trial is 'enforced' people will leave it i.e. if randomised to Methadone when you want Buprenorphine – you would leave the trial
- Has the Mortality Rate in people not on a script been measured?

PPI for NIHR OST Project

10th August 2016

Blackpool Horizon Drug and Alcohol Service

3 focus groups

Group 1

2 staff (1 outreach, 1 HR)

5 service users (1 recently drug free, 1 Buprenorphine, 3 Methadone) 2 women 3 men **Group 2**

2 Staff (Addaction Navigator Service)

1 service user (Methadone) Male

Group 3

2 Staff (1 Delphi prescribing service, 1 ADS Horizon Outreach)

4 service users (3 Methadone, 1 recently drug free) all men

Question 1

What do you think of the findings? (With particular reference to the 1st four weeks on treatment & 1st four weeks after treatment)

Service User Comments:

- Chaos doesn't stop just because you start a 30 ml Methadone script
- Difficult on provide a clean urine (using Methadone), Lifestyle doesn't change I was using on top of Methadone
- Given Methadone script and nothing else is looked at (*no psycho social interventions)*
- Keep upping dose until you provide a clean sample (*i.e. keep on using on Methadone at the beginning)*
- If starting dose is low i.e. 30 ml, which it is in Blackpool and you have£ 70-80 heroin habit you know it won't hold you so go and use on top
- If you had a machine that could measure amount of heroin (*rather than presence or absence)* in your system it would reduce on top use (*i.e. you could have an accurate amount of Methadone prescribed)*
- Prescribers need to be braver and titrate up quicker
- Start on a higher dose (use a blood test)
- Buprenorphine is more expensive you have to work harder to get it – I was lucky and had a good key worker so I got it (9 years ago)
- I had to beg to get off Methadone and on Buprenorphine – was stable and stuck on Methadone for 6 years
- Best key workers are ex users
- Now its easier to get on Buprenorphine *(all service users felt that until recently it had been very difficult to get PX for Buprenorphine in their area)*

- I'm on medication for MH problems & 80mls Methadone
- When people come off scripts they are not given enough support to manage. If support not there, people will use
- People are often depressed after they stop their script – it's a dangerous time – same if coming off Buprenorphine or Methadone
- No point in using on Buprenorphine
- Less chance of OD because Buprenorphine is a partial blocker – they say that but…
- When I first went on Buprenorphine it made me cheerful / chirpy and I had an appetite – didn't want to use
- People I know who have died on Methadone were using lots of other things too; Pregabalin & alcohol
- Subutex (not Buprenorphine) made you want to do things – be more active
- I don't think its right (the data), I think it is safer if you're on Methadone script and using on top
- I can see why Methadone is higher risk (because) people use on top
- Lots of people have their hit first and then Methadone on top to get the buzz

Staff Comments:

- Looking back, people (clients) didn't have much of a say – people were reduced against their will. (They) may not have had a choice of Buprenorphine or Methadone either
- Not surprised at the findings
- It's been easier to get Buprenorphine since the Recovery model came in
- Response to first 4 weeks off: may be because people have other health issues Data didn't look at MH issues

Response to increased risk from Methadone in weeks 1-4 off script Service User Comments:

- People on Methadone have other health issues *(implication that these have not been treated during using/scripting time and come on top when you detox)*
- They (*researchers)* didn't look at mental health problems – I am on medication for MH problems and script 80 ml Methadone.
- When people come off script and are not given enough support (*psychosocial*) then people will use
- People are often depressed when they come off scripts it's a dangerous time – same for Methadone and Buprenorphine

Question 2
What important differences could there be between people starting OST with Methadone or Buprenorphine?

Service User Comments:

- Buprenorphine is a lot 'cleaner' drug to come off when on Buprenorphine you don't feel lost
- I started on Buprenorphine once – it made me feel sick so I asked to change to Methadone – wish I had stayed on Buprenorphine because Methadone dragged me down.
- Methadone made me feel embarrassed /stigma in pharmacy, people know what I am in for. Self esteem goes down on Methadone (*Methadone is for people who don't have much hope and makes you feel like that)*
- If your self esteem is quite good you would want Buprenorphine
- If you are clear and want to move forward you would ask for Buprenorphine
- If you don't want stop you would go for Methadone
- Methadone took me a step back, made me think about how I'm a heroin user
- People on Buprenorphine probably don't use on top
- People on Methadone know that you can use on top so will do
- I know lots of people on Buprenorphine – they stop using
- Most people I know on Methadone are still using
- People would prefer to withdraw from Buprenorphine
- Having had a negative experience of Methadone withdrawal would choose to withdraw on Buprenorphine
- Best to give up on top use in order to swop to Buprenorphine for easier withdrawal
- Binge / Giro using: If you are on Methadone you don't have to plan it – can just do it. If you are on B you have to plan it – might just continue the pattern of planned using after detox – may explain slightly increased risk for Buprenorphine in first 4 weeks off script
- People on Buprenorphine have lost relationship with Heroin, a lapse will have more consequences – don't know local strength etc.,
- People who ask for Methadone may be people without much else going on. I know on Methadone I can choose to use on top
- If I wanted to sort my life out I would ask for Buprenorphine
- Subutex – can detox without noticing – could be risky

Staff Comments:

- More people on Methadone mix with other drugs. People on Methadone less fearful of OD'ing – people think they can use a lot. People on Buprenorphine more fearful – less on top use

- Anyone using significantly more street opiates will be prescribed Methadone to stabilise them – then will be switched to Buprenorphine

- If someone is using 10 bags a day, difficult to get them started on Buprenorphine

Question 3

Should everyone be started on Buprenorphine and then offered a choice of Methadone or Buprenorphine after 4 weeks?

Service User Comments

- You should be offered a choice at the very beginning – "What do you (client) want"
- I don't think Keyworkers are listening – SU's must have a choice
- People have to be put on Methadone if they are injecting – lots can't start on Buprenorphine
- Assessment is a tick box and then you are told you need to start on Methadone "I'll start you on Methadone, then if you give a clean sample you can move to Buprenorphine"
- I went on Suboxone first and opiates went out of my head, then got put on Methadone (because Suboxone too expensive) and I started using
- No – should have a choice but doctors will have the final choice
- I would really try to understand / find out how much people are using then give them a choice
- People should be seen more often by keyworkers
- Individuals must have a choice
- Yes they should be started on Buprenorphine but Buprenorphine is not the same as old Subutex – doesn't perk you up
- I reckon Buprenorphine is a better choice – Methadone is bad for you – it's nasty but you can use on top – it's (a trial) a good idea
- Sometimes people come off Buprenorphine too quickly – feels easy, so think they can just use gear again
- Precipitated withdrawal 10-14 days after stopping Buprenorphine – can get withdrawal symptoms again and panic and use and OD

Staff Comments:

- "I think everyone should be given a choice despite the evidence"
- "I'm an evidence girl" – I'd go with starting on Buprenorphine
- We agree – especially for treatment naïve people
- I think Buprenorphine is safer, so probably a good idea

Question 4
Should there be more studies to test the observation that Buprenorphine is safer than Methadone? What do you think of these 2 options for a study?

Service User Comments:

- I like the second option – but don't see the point of randomisation – if people want to join (the trial) it's because people want Buprenorphine anyway
- I'd accept a trial, but a lot of people wouldn't want a trial
- The risk of a cluster trial is that people will opt out of OST altogether
- Yes, it (the data) should be tested further

- Trials – I wouldn't like to be randomised / If I knew what I wanted I wouldn't want a trial
- People are scared of coming off – wouldn't accept Buprenorphine if they were randomised to it if that's not what they wanted
- I have heard that people on Methadone then changed to Buprenorphine have had problems with their hearts

Staff Comments:

- Anything that will help should be researched – but should look at regional differences in how px are started and compare OD & all cause mortality rates across the country
- RCT would be difficult because of regional differences
- There may be an age difference with younger people preferring to start on Buprenorphine and older people starting on Methadone
- I think they automatically start you on Methadone in Blackpool
- Problem for people collecting OST from specialist prescribers – centralised, it's very hard to get them to attend GP for other health issues – a lot of untreated illnesses – festering e.g. leg ulcers not treated at specialist providers COPD, embolisms, DVT
- Look at link between HOW OST is provided across regions
- Go with RCT because there is a choice
- If there is no choice there will be no engagement with treatment
- Very difficult if the doctor makes the decision (of Buprenorphine or Methadone) regardless of what you want as a keyworker says the client wants – ruins the relationship & the client disengages

Question 5

Any other views or comments on the study?

- What's missing is the psycho social support whilst on scripts – doesn't matter what you are on
- Genuine clients were penalised because of others messing around i.e. Methadone on the streets and doctors insisting on supervised (scripts) all the time so people dropped out *(explanation for increased deaths immediately after treatment with Methadone)*

Facilitators Observations:

Have regional differences in patterns of prescribing been correlated with outcomes NB. Difference between Bristol & Blackpool – In Blackpool reports that more or less everyone starts on Methadone and then switched to Buprenorphine <u>if client insists</u>

Staff at Addiction Dependency Solutions (ADS) Blackpool: Impression that Methadone is 1st line of treatment provided by Delphi which is a private prescribing organisation – no more key working – seen by doctors

Horizons (Blackpool) has contract with 21 day turnaround to start OST – 7 day to start alcohol treatment

Lay Summary and Discussion (provided by MH)

- People who inject drugs (PWID) such as heroin have a risk of death >10 times higher than the general population. Overdose is the most common cause of death among PWID.

- Opioid substitution treatment is the most effective treatment for heroin injectors, most commonly methadone or buprenorphine. Several recent studies have highlighted that there is a period of very high mortality risk in the first few months immediately after treatment cessation – and there may be an elevated risk also in the first few weeks of OST.

- In the UK despite an increase in OST the number of drug related deaths has not fallen and is cause of public health concern.

- We have conducted a series of analyses of patients prescribed OST in primary care to consider how OST might be changed to be more protective and reduce drug related deaths in the population.

- We compare the mortality risk for people prescribed buprenorphine or methadone.

Summary Results

- We analysed data from primary care on 11,033 patients and 26,546 OST episodes – 17,373 methadone and 9173 buprenorphine.

- There were a total of 587 all cause deaths during or within 1 year of finishing OST – giving an overall mortality rate of 1.93 deaths per 100 person-years (nearly 2% annually).

- Information on overdose deaths was available for 5935 patients (54%), 15,600 episodes (9550 methadone and 6050 buprenorphine and involved 87 deaths – mortality rate 0.53 deaths per 100 person-years (0.5% per year).

- There were differences in the mortality risk during periods on and off treatment as shown in the two tables below:-

	All cause mortality				Overdose Deaths mortality			
Period	Deaths	Interval	MR	p	Deaths	Interval	MR	p
On 1-4 weeks OST	48	1541	3.11	<0.0001	8	897	0.89	<0.0001
On rest of time OST	179	18240	0.98		27	9165	0.29	
Off OST 1-4 weeks	165	1730	9.54		18	1044	1.72	
Off OST rest of time	195	8900	2.19		34	5257	0.65	

Interval: person-years at risk; MR mortality rate (deaths/100 person-years – like a %)

Period	All cause				Overdose			
	IRR	95% CI		p	IRR	95% CI		P
On 1-4w	3.17	2.31	4.37	<0.0001	3.03	1.38	6.66	<0.0001
On rest	1 (ref)				1 (ref)			
Off 1-4w	9.72	7.85	12.03		5.85	3.22	10.63	
Off rest	2.23	1.82	2.74		2.20	1.33	3.64	

IRR – incidence rate ratio – relative measure of risk of all cause or OD death compared to being on OST from 4 weeks.

- The lowest risk period is on OST after the first month of OST – compared to this period the risk of OD is 3 times higher in first month, nearly 6 times higher in first month off treatment, and twice as high in the rest of time off OST. Similarly the risk of all cause mortality is 3 times higher in the first month on treatment, nearly 10 times higher the month after OST drop out or discharge, and 2 times higher the rest of the time in the community – compared to the lower risk period during OST from week 4 onwards.

- There are important differences in mortality risk between people on buprenorphine and methadone shown in the tables below:-

Period	OST drug	All cause mortality				Drug related mortality			
		Deaths	Interval	MR	p	Deaths	Interval	MR	p
On 1-4w	Methadone	46	1036	4.44	**0.0001**	7	563	1.24	**0.2561**
	Buprenorphine	2	505	0.40	0.0144	1	334	0.30	0.5583
On rest	Methadone	157	14639	1.07		23	6924	0.33	
(ref)	Buprenorphine	22	3601	0.61	n/a	4	2242	0.18	n/a
Off 1-4w	Methadone	150	1091	13.75		10	620	1.61	
	Buprenorphine	15	639	2.35	0.0007	8	424	1.89	0.2084
Off rest	Methadone	153	6054	2.53		28	3379	0.83	
	Buprenorphine	42	2846	1.48	0.9309	6	1878	0.32	0.7011

Period	OST drug	All Cause				Overdose			
		IRR	95% CI		p	IRR	95% CI		P
On 1-4w	Methadone	1 (ref)			**0.0001**	1 (ref)			**0.2956**
	Buprenorp.	0.09	0.02	0.37	0.0144	0.24	0.03	1.96	0.5035
On rest	Methadone	1 (ref)				1 (ref)			
(ref)	Buprenorp.	0.57	0.36	0.89	n/a	0.54	0.19	1.56	n/a
Off 1-4w	Methadone	1 (ref)				1 (ref)			
	Buprenorp.	0.17	0.10	0.29	0.0007	1.17	0.46	2.98	0.2805
Off rest	Methadone	1 (ref)				1 (ref)			
	Buprenorp.	0.58	0.41	0.82	0.9309	0.39	0.16	0.93	0.6382

P values in bold reflect the interaction effect with 3 dfs. Other p values compare IRR at one time with IRR for on rest.

- There is evidence that the risk of overdose and all cause mortality is lower in the first 4 weeks of treatment on buprenorphine compared to methadone. And some evidence that risk of all cause mortality is lower for patients on buprenorphine at other periods as well.

- These mortality rates and measures of difference (IRR) have not been adjusted for differences in patient characteristics and so must be interpreted very cautiously.
- There are many different factors between methadone and buprenorphine treatment.

Duration of Treatment:- The durations of treatment episodes were highly skewed with methadone having longer durations on average than buprenorphine.

Duration	Methadone	Buprenorphine
≥3 weeks	76.30	65.55
≥3 months	53.71	33.44
≥6 months	39.43	21.08
≥1 year	26.71	12.22
Mean (days)	360	173
Median (days)	110	40
N (episodes)	17373	9173

Other Factors:- There are differences also in patient characteristics and GP prescribing habits by:- sex, age, calendar year, co-morbidity, region, co-prescription of benzodiazepines, co-prescription of Gabapentin/Pregabalin, history of self-harm, overdose, alcohol problems, prison or homelessness reported in GP notes, number of OST patients per practice and size of practice.

- We do not have other important information on the patients – such as severity of addiction, recent imprisonment, current housing status, reason for OST.

- However, after adjusting for these factors the differences between methadone and buprenorphine are not removed – if anything they are strengthened for all cause mortality (see table below).

		All Cause				Overdose			
9Period	OST Type	Adjusted IRR	95% CI		p	Adjusted IRR	95% CI		P
On 1-4w	Methadone	1 (ref)			**0.0002**	1 (ref)			**0.2631**
	Buprenorp.	0.04	0.01	0.16	0.0136	0.27	0.03	2.07	0.5599
On rest	Methadone	1 (ref)				1 (ref)			
(ref)	Buprenorp.	0.26	0.16	0.43	n/a	0.53	0.18	1.59	n/a
Off 1-4w	Methadone	1 (ref)				1 (ref)			
	Buprenorp.	0.07	0.04	0.12	0.0002	1.32	0.48	3.64	0.2076
Off rest	Methadone	1 (ref)				1 (ref)			
	Buprenorp.	0.21	0.14	0.32	0.5225	0.41	0.16	1.05	0.7174

IRR Incident rate ratio. Adjusted for gender, age, year, comorbidity, region, treatment period and OST type.

- We have less data on OD and so the analyses are slightly underpowered. The differences in mortality risk between Buprenorphine and Methadone follow similar pattern to all cause mortality except for the comparison between methadone and Buprenorphine in first 4 weeks after treatment. However, some of the differences between Buprenorphine and Methadone also may be due to unmeasured confounding - so we need to be careful when interpreting these findings.

We would like to consult with users and drug workers on these findings:-

1. What other important differences could there be between people starting Buprenorphine vs Methadone?

2. What do you think of the findings? What else needs to be done to support hypothesis that Buprenorphine is safer than Methadone?

3. Would you participate, support and be interested in a study that induces all patients in a research study onto Buprenorphine then from 4 weeks allows patients to choose to continue with Buprenorphine or switch to Methadone?

4. What interventions / communication is needed to support such a study with users and drug workers?

5. How do we ensure people in Buprenorphine or Methadone are retained in treatment?

6. Other views/comments

Appendix 4 Registered patients within Clinical Practice Research Datalink and the UK by year

	CPRD patients by country (0000)					Registered patients by country (0000)				
Year	England	Wales	Scotland	Northern Ireland	UK	England	Wales	Scotland	Northern Ireland	UK
1998	236	19	17	8	280	5112	300	536	176	6124
1999	290	25	21	10	346	5090	298	537	177	6102
2000	329	30	24	12	395	5134	301	535	178	6148
2001	359	34	31	14	439	5125	301	535	177	6139
2002	384	35	38	16	473	5152	304	535	178	6168
2003	393	38	48	16	495	5271	302	534	178	6286
2004	403	40	51	17	511	5253	304	537	179	6273
2005	409	41	51	17	518	5282	305	539	179	6305
2006	419	41	52	17	529	5324	309	541	181	6355
2007	422	43	52	17	534	5307	309	542	183	6342
2008	417	44	53	16	529	5361	311	547	185	6404
2009	414	44	53	16	527	5414	313	550	187	6464
2010	413	44	53	16	526	5502	315	552	188	6557
2011	399	44	54	16	513	5531	316	553	190	6589
2012	386	45	54	16	500	5574	317	555	191	6637
2013	379	47	54	16	495	5601	318	557	192	6667
2014	335	46	55	16	451	5647	317	560	194	6718

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